Ablative Fractional CO_2 Laser for Facial Atrophic Acne Scars

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Abstract

Ablative fractional carbon dioxide laser resurfacing is a well-established treatment for acne scars. However, there are limited consensus and guidelines regarding the procedure, such as its treatment plan, efficacy, and safety. In this study, we performed a systematic review to assess the efficacy and safety of the fractional carbon dioxide laser treatment procedure, and to provide evidence-based recommendations concerning its practical use on atrophic acne scars. A comprehensive search was performed in, EMBASE, Ovid, Web of Science, and Cochrane databases, using the keywords "scar(s)," "acne vulgaris," "carbon dioxide," and "fraction* laser(s)" for the period from January 1987 to December 2016. The initial literature search identified 337 articles. The final selection included 30 studies: 12 retrospective studies and 18 prospective randomized clinical trials. Ablative fractional carbon dioxide laser is an effective therapy for the treatment of acne scars. The treatment session, interval, and parameters should be customized for each patient. Combination therapy should be considered for ice-pick type acne scars. The use of dermocosmetics in pre- and postoperative care may be beneficial to patients.

Keywords

- acne scars
- carbon dioxide laser
- fractional lasers

Acne scarring—a common consequence of acne—results from the net gain or loss of collagen fibers and subcutaneous fat during inflammatory acne vulgaris healing. The incidence of acne scarring has not been extensively studied, but it is estimated to affect approximately 95% of acne patients.[1] Having acne scars can be emotionally and psychologically distressing to patients, which in turn can be a high-risk factor for suicide.[2]

Studies have also shown that suffering from acne scars is linked to poor self-esteem, reduced daily activities and social interactions, and unemployment.[3,4] Acne scars are classified into three types: atrophic scar, hypertrophic scar, and keloid. Atrophic acne scar can be further divided into three subtypes: ice-pick scar, rolling scar, and boxcar scar according to their width, depth, and three-dimensional (3D) architectures.[5,6] A quantitative global acne scarring grading system is the standard for the assessment of disease load and severity of acne scarring, and atrophic acne scar can be classified into mild, moderate, and severe scarring according to its severity.[6]

Many treatment options are available to improve atrophic acne scars, including chemical peels, dermabrasion/microdermabrasion, punch grafting, tissue fillers, needling, nonablative fractional resurfacing (NAFR) lasers, and ablative lasers. However, these treatments are often limited in variable and operator-dependent efficacies, temporary nature of clinical improvements, and adverse effects.[7,8]

Carbon dioxide (CO_2) laser is a well-established and effective treatment for atrophic acne scars. The laser at a wavelength of 10,600 nm is absorbed by the water in intracellular tissues and can selectively heat and vaporize superficial skin.[7] Through controlled heating of dermal collagen, the traditional CO_2 laser can eliminate the fragmented collagen matrix and therefore promote new collagen production and subsequently improve scar appearance.[9] However, the procedure is associated with high risk of

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complications and side effects, such as lengthy recovery time, prolonged erythema, scars, hypopigmentation, and postinflammatory hyperpigmentation (PIH), especially for patients with a darker skin phototype.[10,11]

Fractional photothermolysis (FP), a new technique of skin rejuvenation, was designed to overcome these problems. To achieve homogeneous thermal damage at a particular depth within the skin, FP creates microscopic thermal wounds—referred to as the microscopic thermal zone—and specifically spares tissues surrounding each wound.[12] Ablative fractional carbon dioxide laser (AF CO_2) treatment combines CO_2 ablation with the FP system and represents a safe and effective treatment modality for acne scarring.

Compared with conventional ablative CO_2 lasers, the AF CO_2 method can provide rapid reepithelialization from surrounding undamaged tissues, thus resulting in faster recovery, reduced downtime, and greatly improved side effects for patients.[13–15] Magnani and Schweiger reviewed the efficacy and safety of AF CO_2 for the treatment of atrophic scarring secondary to acne vulgaris.[16]

The goal of this review was to establish individualized treatment guidelines after analysis of the treatment procedures.

Methods

Entry Criteria and Elimination Criteria

To provide a comprehensive collection of related studies, our entry criteria included not only randomized controlled trials, but also published clinical studies, case series, and case reports relevant to the topic. Studies that were not available in English or did not report therapy results separately for acne scars were excluded. Reviews, abstracts, posters, oral presentations, editorials, and studies that did not specifically evaluate or comment on the efficacy of AF CO_2 treatment on acne scars were also excluded.

Data Sources and Search Strategy

We systematically searched the English literature in, EMBASE, Ovid, Web of Science, and Cochrane databases to identify relevant trials. The search terms were "scar(s) (title/abstract/keywords)" and "acne vulgaris (Mesh terms)" and "carbon dioxide" and "fraction* laser(s)." The selection procedures are shown in ►**Fig. 1**.

Results

The literature search yielded 337 unique articles; 30 articles met our inclusion and exclusion criteria, comprising 12 retrospective studies (case series and case reports)[17–28] and 18 prospective randomized clinical trials.[29–46]

Patient Characteristics

This review covered a total of 512 patients enrolled in 30 studies (including 407 Asian patients in 24 studies); the patient characteristics are shown in ►**Table 1**. The mean age of the enrolled subjects ranged from 22 to 40 years.[18,19] The severity of acne scars was mostly accessed according to the Goodman and Baron quantitative global scarring grading system,[6] with three studies[33,38,45] based on the ECCA (échelle d'évaluation clinique des cicatrices d'acné) grading scale.[47] Thirteen studies included patients with Fitzpatrick skin type III to IV and seven studies included type IV patients only.

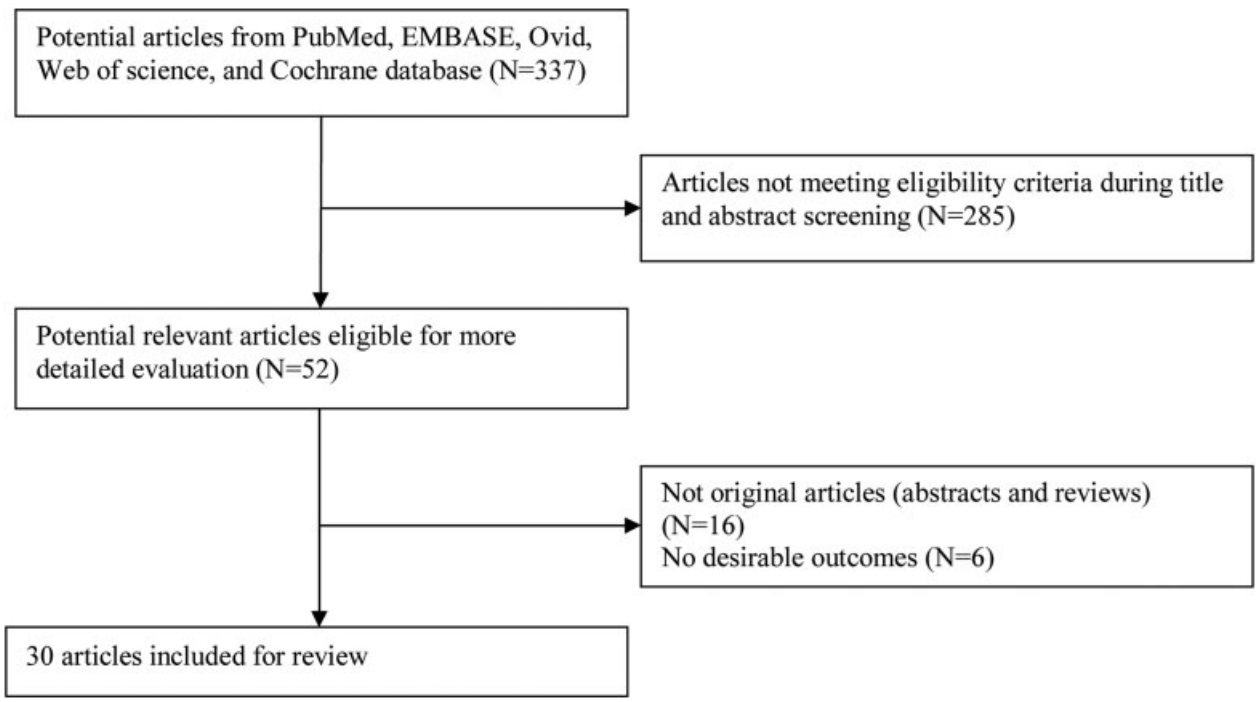

Fig. 1 Flow diagram illustrating the paper selection process.

Table 1 Patient characteristics

Study	Year	Country	Number of patients	Sex ratio (M/F)[a]	Age (mean or range in y)	Fitzpatrick skin type	Atrophic scars severity[b]	Atrophic scars types[c]
Chapas et al[17]	2008	United States	15	NA	28–58	I–IV	Moderate to severe	Boxcar, rolling, ice pick
Walgrave et al[18]	2009	United States	30	NA	40	I–V	Moderate to severe	NA
Qian et al[19]	2012	China	31	20/11	22.0	III–IV	Mild to severe	Boxcar, rolling, ice pick
Hsiao et al[20]	2013	Taiwan	25	19/6	30.4	III–IV	Mild to moderate	Boxcar, rolling, ice pick
Cho et al[21]	2009	Korea	20	7/13	27	IV	Mild to severe	NA
Huang[22]	2013	China	44	13/31	26	IV	Moderate to severe	NA
Trelles et al[23]	2011	Spain	10	NA	NA	III–IV	NA	NA
Ahmad et al[24]	2012	Pakistan	20	3/17	23	III–IV	Mild to moderate	NA
Manuskiatti et al[29]	2010	Thailand	13	5/8	34	IV	Mild to moderate	NA
Kim et al[25]	2014	South Korea and China	20	9/11	23.9	III–IV	NA	NA
Hedelund et al[30]	2012	Denmark	13	6/7	33	I–III	Moderate to severe	NA
Schweiger and Sundick[27]	2013	United States	6	5/1	26.5	NA	NA	NA
Wang et al[26]	2010	Singapore	5	4/1	27	IV	Moderate to severe	NA
Alajlan et al[28]	2011	Saudi Arabia	37	NA	NA	III–IV	Mild to severe	NA
Cho et al[35]	2010	South Korea	8	8/0	21.3	IV	Mild to severe	Rolling, boxcars, ice pick
Manuskiatti et al[46]	2013	Thailand	24	NA	29.5	IV	NA	Shallow or deep boxcar
Reinholz et al[36]	2015	Germany	14	9/5	28.6	NA	Severe	Rolling, boxcar, ice pick
Asilian et al[37]	2011	Iran	32	NA	26.3	II–IV	Moderate to severe	Rolling, boxcar, ice pick
Zhang et al[38]	2013	China	14	11/3	26.4	III–IV	Mild to severe	NA
Azzam et al[39]	2013	Egypt	10	NA	18–38	III–IV	NA	Rolling, boxcars, ice pick
Ahmed et al[40]	2014	NA	14	NA	22.7	II–V	NA	Ice pick
Cameli et al[41]	2014	NA	6	NA	NA	NA	NA	Superficial, rolling

(*Continued*)

Table 1 (*Continued*)

Study	Year	Country	Number of patients	Sex ratio (M/F)[a]	Age (mean or range in y)	Fitzpatrick skin type	Atrophic scars severity[b]	Atrophic scars types[c]
Faghihi et al[42]	2016	China	16	4/12	36.8	II–IV	Moderate to severe	Rolling, boxcars, ice pick
Gawdat et al[43]	2014	NA	5	2/3	24.8	III–IV	Mild to severe	NA
Lee et al[44]	2011	South Korea	14	10/4	28.1	III–IV	Moderate to severe	NA
Zhou et al[45]	2015	NA	13	NA	NA	NA	NA	NA
Kim and Cho[31]	2009	South Korea	20	11/9	24.5	IV–V	Mild to severe	NA
Jung et al[32]	2010	South Korea	10	10/0	22.2	IV	Mild to severe	NA
Yuan et al[33]	2014	China	10	10	22–31	III–IV	Moderate to severe	NA
Bjørn et al[34]	2014	NA	13	NA	18–60	I–III	Moderate to severe	NA

Abbreviations: F, female; M, male; NA, not answered.
[a]Patient in the fractional carbon dioxide laser treatment group.
[b]Severity of the scar was determined according to Goodman and Baron.[6]
[c]Type of the scar was determined according to the report by Jacob et al.[5]

Most of the exclusion items for patient selection are listed in ►**Table 2**, while exclusion criteria were not mentioned in four studies.[22,23,27,28] Isotretinoin use was excluded in 26 studies, except in the Kim et al[25] study where all patients received oral isotretinoin ranging from 10 to 40 mg/d. A history of keloid scars was also excluded in the Walgrave et al, Ahmad et al, and Gawdat et al studies.[18,24,43]

Treatment Procedures

All treatment procedures are summarized below. First, treatment areas were cleaned with a mild cleanser. Then, topical anesthesia such as local anesthesia and facial nerve blocks or oral pain-killer were applied before treatment.[17,18,20–22,25,26,29,30,32–35,38,42,43] Patients were prepared with an intravenous catheter in case extra analgesia or sedation was required.[23] Next, alcohol or acetone was used to degrease the skin before the treatment began.

To help mitigate the pain and reduce the burning sensation experienced during the treatment, forced air cooling system or cold air flow[18,21,23,31,35] was constantly applied to the treatment area, and wet, cold gauzes or ice packs[20,22,29,33,42–44] were applied immediately after the operation. Cleaning of the treated site with tap water after the treatment was allowed in two studies,[26,38] but was not permitted until 24 hours or later in four studies.[22,23,25,33] Postoperatively, a moisturizing cream was applied to promote wound healing and prevent dryness.[20–23,25–27,29,31,32,34,35,38,39,41,46]

Prophylactic and postoperative antiviral agents were recommended for subjects with a documented history of herpes labialis only[21,29,32,34,35,38,44] or for all patients.[18,25] In two studies,[23,26] no oral antiherpes medication was recommended. Prophylactic antibiotics were given to all patients in three studies,[17,18,29] while a topical antibiotic cream was recommended after the treatment in several other studies.[19,25,39,41–43]

To prevent an inflammatory reaction and reduce facial edema, oral steroids,[21,32,35] or topical steroid creams were prescribed for the first several days.[18,25,33,39] Nearly all the studies recommended daily use of a broad-spectrum sunscreen to avoid overexposure to sunlight[19–26,29,32,33,35,38–40,42,43,46] immediately after the treatment, while the use of sunscreen until complete healing of crusting was recommended in five other studies.[21,25,29,33,46] A recombinant human epidermal growth factor containing hydrogel was applied four times daily for 1 week in two studies.[22,33] Postoperative care was not specified in three articles.[28,36,37]

Treatment Sessions and Intervals

A summary of the 30 reviewed studies is shown in ►**Table 3**. Eight case series, involving a total of 95 patients, showed the benefit of CO_2 laser ablation with a single session.[20,21,23,27,32,33,35,41] At the 4-week follow-up, the clinical improvement based on the depth of scar assessed by both the physicians and patients was rated at over 60%.[27] In Trelles et al's[23] study, all patients had 26 to 50% improvement at 2 months. All patients in the Cameli et al[41] study were reported to have more than 25% clinical improvement 3 months after treatment. Similarly, at the 3-month follow-up, the quartile grading scores in the Cho et al,[21] Hsiao et al,[20] and Cho et al[35] studies were 2.41, 2.4, and 2.5, respectively, corresponding to 26 to 50% overall improvements.

Table 2 Exclusion of patients

Items of exclusion	References
Pregnant or lactating	17–21,25,29–38,41–46
Isotretinoin use (oral retinoids within the preceding 12 or 6 mo or topical use)	17–21,24–26,29–36,38–46
History of keloid scar formation	17,19–21,25,26,29–42,44–46
Cosmetic procedures (filler injections, botulinum toxin A, ablative/nonablative laser skin resurfacing procedures, chemical reconstruction of skin scars using trichloroacetic acid, collagen induction therapy using a microneedle therapy system) within the previous 6 or 12 mo	17–21,24–26,29–35,37,38,40,42,44,46
Undergoing immune suppression	19,21,32,33,35,37,38,40,43
Active infections (localized or systemic infections status)	17–19,36,38,40,44,45
History of photosensitivity	19,25,26,30,38,39
Pigmentation after recent exposure to the sun or solarium	25,30,34
Current anticoagulative medication	25,30,41,45
History of carcinoma or cancer lesions	26,38,45
Systemic disease (diabetes or hypertension), collagen disease, diabetes	39,41,42,44,45
Active dermatitis, warts	38,44,45
Herpes simplex infection (during the previous 6 mo)	31,34,40,42,45
Allergies to lidocaine	17,18
Smoking	17,18,26
Corticosteroids	45
Fitzpatrick skin type of VI	18
Deep boxcar and ice-pick acne scars, active acne	31,41
Younger than 18 y	39

A total of 18 published articles reported treatments of two to seven sessions at the intervals of 4 to 12 weeks.[17–19,24,26,28–31,36–40,42–46] A total of 30 patients (16 women, 14 men) received two split-face treatments at 4-week intervals in two studies.[42,44] Wang et al[26] and Manuskiatti et al[46] treated 25 patients with two sessions at 8-week intervals.

In five studies, 72 patients were treated with three sessions of AF CO_2 at 4-week intervals.[30,31,39,43,45] At the 1-month follow-up after the last treatment, objective clinical assessment scores were 1.89 and 2.0 based on a quartile grading in the Kim and Cho[31] and Zhou et al[45] studies, respectively. The final assessment was performed 3 months after the last treatment, when all patients reached over 50% improvement according to the physicians' assessment,[43] whereas a 70% improvement was achieved in the Azzam et al[39] study.

The mean clinical score of texture and atrophy on a 0 to 10 numerical scale improved from 6.15 and 5.72 (before treatment) to 4.26 and 3.97 ($p < 0.0001$) at 3 months and 3.89 and 3.56 ($p < 0.0001$) at 6 months following the last treatment.[30] In six studies,[17–19,28,29,38] patients were treated with three sessions of AF CO_2 at 8-week intervals. At 3-month follow-up after the last treatment, the mean quartile grading scores were 1.42 and 2.46, respectively, in the Chapas et al[17] and Walgrave et al[18] studies. The percentages of patients achieving 25% improvement were 70, 85, and 84.6%, respectively, in the Qian et al,[19] Manuskiatti et al,[29] and Alajlan et al[28] studies at 3 months following the last treatment.

According to the ECCA scores,[47] the scars improved from 48.8 ± 15.1 to 19.9 ± 7.9 (59.2% improvement) in the Zhang et al[38] study at 6 months after the last treatment. The longest follow-up time frame was 12 months after the last treatment (in Qian et al's study[19]), where 80.6% of the patients had more than fair improvements, which was a figure higher than that recorded at the 3-month follow-up.

Three articles reported AF CO_2 treatment in 60 patients with four or more sessions at 4-week intervals[36,37,40]: one prospective clinical trial[24] (conducted for six sessions at 4-week intervals, where an average of 71% improvement was observed at the 6-month follow-up) and two retrospective reviews.[22,25]

The Bjørn et al[34] study conducted a split-face trial to compare the influence of treatment intervals between 1-month and 3-month after two treatments. The results indicated that the different intervals did not affect the improvement of scar atrophy or the occurrence of postoperative adverse effects. It was suggested that 3-month could be a more appropriate treatment interval.[34]

Treatment Parameters

In terms of the treatment area, full face laser treatment was conducted in 12 studies.[17,18,21–23,29,32,33,35,37,38,43] A so-called "focal acne scars treatment (FAST)" method was conducted in the Schweiger[27] study where only the acne scars were treated, and the normal skin was left untouched. All

Table 3 Summary of reviewed studies

Study/study type	CO_2 facility	Energy/density (level)[a] or coverage/ spot size	No. of passes/ treatment area	No. of sessions/ intervals/ follow-up (mo)	Primary results/ conclusions
Chapas et al[17]/ case series	Reliant Fraxel re: pair laser prototype	20–100 mJ/ 200–1,200 MTZ/cm^2/ 120 μm	2 or 3 passes/full face	2–3 /1–2 mo/1, 3	MQGS were 2.42/ 4 and 2.46/4 for subjects and investigators Immediate erythema was graded as mean 2.92/4
Walgrave et al[18]/ case series	Reliant Fraxel re: pair laser prototype	20–100 mJ/ 600–1,600 MTZ/cm^2	1 pass/full face	1–3/4–12 wk/1, 3	MQGS was 1.73/4 and1.42/4 for investigator at 1 and 3 mo follow-up Average pain score was 5.9/10
Qian et al[19]/ case series	Lumenis ActiveFx, UltraPulse 5000	150–200 mJ/5–6/ 1.2 mm	1 pass/full face or cheeks or forehead	3/2 mo/3, 12	Patients with excellent, good, fair, and poor improvements were 4 (12.9%), 8 (25.8%), 13 (41.9%), and 6 (19.4%) at 12 mo follow-up 4 patients exhibited posttreatment and transient PIH
Hsiao et al[20]/ case series	Lumenis UltraPulse Encore fractional CO_2 laser	Deep FX 12.5–15 mJ/ 2–3/0.12 mm	Cheeks or nose	1 session/1, 3	MQGS was 2.41/4 for physicians at 3 mo follow-up Side effects were minimal and had mostly resolved by 3 mo
Cho et al[21]/ case series	Lumenis UltraPulse Encore fractional CO_2 laser	Deep FX 10–20 mJ/ 2 + Active FX 50–100 mJ/2	1 pass/Deep FX for acne scars + Active FX/ full face	1 session/3	MQGS was 2.4/4 for physicians Patients' satisfaction revealed that 60.0% were very satisfied or satisfied Mean duration of posttherapy crusting or scaling was 6.3 d Posttherapy erythema lasted 2.8 d
Huang[22]/ retrospective review	Lumenis UltraPulse Encore fractional CO_2 laser	Active FX 100–150 mJ/5–7; Deep FX10–15 mJ/ 10–15%; Active FX 100–125 mJ/1–2/ 120 μm for Deep FX and 1.3 mm for Active FX	4–5 passes/Deep FX for acne scars + Active FX for full face	2–7/2–6 mo/3	64% had an improvement between 51 and 75% Average overall improvement was 52.50% Edema usually resolved within 3 d

Table 3 (*Continued*)

Study/study type	CO_2 facility	Energy/density (level)[a] or coverage/ spot size	No. of passes/ treatment area	No. of sessions/ intervals/ follow-up (mo)	Primary results/ conclusions
Trelles et al[23]/ retrospective study	Alma Pixel CO_2 laser system	120 mJ	4–6 passes (scar tissue) + 2 passes (full face)	1 session/2	All patients had fair or good improvements; Erythema free 2 mo after treatment
Ahmad et al[24]/ case series	Max 7000, Korea	10–20 mJ/2–3	1 pass/full face	6/1 mo/6	Average improvement of 71% was observed
Manuskiatti et al[29]/single-blinded RCT	Hørsholm Ellipse Juvia, Ellipse A/S	75–105 mJ/MTZ/ 9.6%/500 μm	1 pass/full face	3/Average 7 wk/ 1, 3, 6	Physicians graded 85% of subjects as having 25–50% improvement Over 50% of patients (8 of 13) rated themselves as having >50% improvement Average pain 8.1/10; PIH was 92.3%
Kim et al[25]/ retrospective study	Lutronic Mosaic eCO_2 laser	30–50 mJ/100–200 MTZ/cm^2	1–2 passes	1–6/> 1 mo/6	All patients achieved moderate-to-much improved scores The results after 6 mo were satisfactory in all patients Complete reepithelialization after 7 d in all patients
Hedelund et al[30]/ intraindividual[b] single-blinded RCT	Hvidovre MedArt 610	48–56 mJ/13%/ 0.5 mm	1pass/cheeks, temporal and chins	3/4–5 wk/1, 3, 6	Scar texture and atrophy by physicians at 6 mo follow-up were 3.89/10 and 3.56/10 Patients' satisfaction scores was 4.5/10 Mild-to-moderate pain
Wang et al[26]/case series	MiXto SX, CA	28 J/cm^2/20%/ 300 μm	1 pass/full face	1 session/2	4 patients had mild improvement; 1 patient had moderate improvement Erythema lasted for a mean of 6 d
Schweiger and Sundick[27]/case series	MiXto SX, Italy	13–14 J/S/15–40%	1or 2 pass/acne scars	1 session/4 wk	3 patients had 60% improvement; 2 patients had 70% improvement; 1 patient had 75% improvement

(*Continued*)

Table 3 (*Continued*)

Study/study type	CO_2 facility	Energy/density (level)[a] or coverage/ spot size	No. of passes/ treatment area	No. of sessions/ intervals/ follow-up (mo)	Primary results/ conclusions
Kim and Cho[31]/ single-blinded RCT	Stratek CoScan-5000	High energy: 50–70 mJ Low energy: 15–35 mJ/20%/ 0.2 mm	1 pass/full face	3/4 wk/3	Observers' grading averaged 5.8/10 and 4.0/10 separately for the treatment with h-AFR alone and l- AFR Subjects' self-grading averaged 6.2/10 and 4.2/10 separately for the treatment with h-AFR alone and l- AFR Laser treatments with h-AFR alone were associated with more erythema, crusts, and hyperpigmentation
Jung et al[32]/single-blinded split RCT	Lutronic Mosaic eCO_2 laser	Low-fluence, high-density: 30 mJ/12.8% High-fluence, low-density 70 mJ/ 12.3% coverage	1 pass/full face	1 session/3	MQGS was 2.47/4 for physicians for low-fluence, high-density CO_2 FS and 3.37/4 for high-fluence, low-density Overall satisfaction levels of the two group were not significantly different
Yuan et al[33]/ single-blinded split RCT	Lumenis UltraPulse Encore fractional CO_2 laser	Deep FX, group A 20 mJ/10% VS 20 mJ/ 20% Group B 20 mJ/10% VS 10 mJ/10%	1 pass/full face	1 session/1, 3	Group A: 8/10 patients showed >50% improvement in both the lower and higher fluence groups; patient satisfaction 5.90/ 10 vs. 5.95/10, average edema duration 3.10 vs. 4.50, mean pain 4.36 vs. 6.12 Group B: 8/10 patients showed >50% improvement in the lower fluence group, 9/10 patients showed >50% improvement in the higher fluence group; patient satisfaction 5.42/ 10 vs. 5.30/10,

Table 3 (*Continued*)

Study/study type	CO_2 facility	Energy/density (level)[a] or coverage/ spot size	No. of passes/ treatment area	No. of sessions/ intervals/ follow-up (mo)	Primary results/ conclusions
					average edema duration 3.50 vs. 2.50, mean pain 4.98 vs. 4.39
Bjørn et al[34]/ intraindividual single-blinded split RCT	Lumenis UltraPulse Encore fractional CO_2 laser	Deep FX 17.5–22.5 mJ/15% +Active FX 105 mJ/ 82%	1 pass/full face	2/1 mo vs. 3 mo/1, 6	No differences between the different treating interval nor the occurrence of postoperative adverse effects Pain 7.23/10 on the first treatment
Alajlan et al[28]/ retrospective study	FX–Lumines, CA	Avg.125 mJ/cm^2/30%	1 pass/full face	Average 2.5/2 mo/3	37% of patients attained $>$ 50% improvement with AF CO_2 lasers Patient satisfaction 65% for AF CO_2 laser; PIH was 41%
Cho et al[35]/single-blinded split RCT	Lumenis UltraPulse Encore fractional CO_2 laser	Deep FX 10–20 mJ/2 Active FX 50–100 mJ/2	1 pass/Deep FX for acne scars + Active FX for full face	1 session/3	MQGS was 2.5/4 for physicians 50.0% of patient were slightly satisfied Mean duration of posttherapy crusting and scaling was 7.4 d, erythema lasted 11.5 d
Manuskiatti et al[46]/single-blinded split RCT	Lumenis AcuPulse	Average 13.75 mJ/5% coverage/10 mm	1 pass	2/2 mo/1, 3, 6	65% of CO_2 sites were rated as $>$ 50% improvement by physicians 60% of CO_2 sites were rated as $>$ 50% improvement in patients Average pain 5.8/10, lasting for an average of 3 h Crusting completely sloughed off in an average of 3.3 d
Reinholz et al[36]/ single-blinded split RCT	MultiPulse by Asclepion Laser Technologies	5–25 J/S/500 μm	1 pass	4/4 wk/1	Severity of the evaluated atrophic acne scars changed from an average of 5.8/10 points to 3.9/10 Reduction of scar depth was 32.7% after treatment Mean pain 5.0/10

(*Continued*)

Table 3 (*Continued*)

Study/study type	CO_2 facility	Energy/density (level)[a] or coverage/ spot size	No. of passes/ treatment area	No. of sessions/ intervals/ follow-up (mo)	Primary results/ conclusions
Asilian et al[37]/ single-blinded RCT	Alma Pixel CO_2 laser system	350 μm	3 passes /full face	4/4 wk/6	Mean percent of scar improvement was 46.6% of patients 37.5% of patients had >50% improvement by physicians PIH resolved spontaneously after 2–3 wk
Zhang et al[38]/ single-blinded split RCT	Alma Lasers Accent	Deep FX mode, 20–25 mJ//2–4	1 pass/full face	3/Average 8 wk/6	59.2% improvement (ECCA scores) 60.6% of patients were very satisfied or satisfied Mean duration of posttherapy erythema and scaling was 5.7 d Average duration of PIH was 45.8 d
Azzam et al[39]/ single-blinded RCT	DEKA SmartXide	15 J/S/800 μm	1 pass	3/4 wk/3	Almost 70% as having moderate scar improvement Mean pain 9 PIH was seen in two patients
Ahmed et al[40]/ randomized, parallel group study	DEKA Ultra-30 Plus: TCA VS AF CO_2	0.9 J/S/0.12 mm	1 pass/acne scar	4/3 wk/6	78.0% of patients had >50% improvement by physicians 86.0% of patients rated their satisfaction as "well" 2 patients developed pustules, and another two patients developed transient PIH
Cameli et al[41]/ single-blinded split RCT	DEKA SmartXide2	30 mJ/500μm	1 pass	1 session/1 wk, 3	30% excellent, 40% good, 30% sufficient by physician evaluation Patient evaluation 25% excellent, 40% good, 34% sufficient, 1% insufficient
Faghihi et al[42]/ single-blinded split RCT	Diosis, Q-ray CO_2	30 mJ/500 μm	1 pass	2/1 mo/4	A fair or good response was seen in 68.8% of patients 43.8% patients

Table 3 (*Continued*)

Study/study type	CO_2 facility	Energy/density (level)[a] or coverage/ spot size	No. of passes/ treatment area	No. of sessions/ intervals/ follow-up (mo)	Primary results/ conclusions
					reported being satisfied or very satisfied Mean duration of edema was ~6.3 d, erythema lasted 4.1 d
Gawdat et al[43]/ single-blinded split RCT	DEKA SmartDOT	15 J/S/2/700 μm	1 pass/full face	3/1 mo/3	All patients achieved >50% improvement by physicians and patients assessment Mean duration of edema was ~3.80 d, erythema lasted 3.87 d PIH 13.3%
Lee et al[44]/single-blinded split RCT	Diosis, Q-ray CO_2	25 mJ/400 MTZ/cm^2/ 150 μm	1 pass	2/4 wk/4	MQGS was 2.3/4 Duration of erythema was an average of 10.4 d Duration of edema was an average of 7.1 d
Zhou et al[45]/split-face RCT	Crius, Han's Laser	8 W/25%	2 passes/acne scars	3/1 mo/1	MQGS was 2.08/4 for patients MQGS was 2.00/4 for physicians

Abbreviations: AF CO_2, ablative fractional carbon dioxide laser; AFR, ablative fractional resurfacing; ECCA, échelle d'évaluation clinique des cicatrices d'acné; MTZ, microscopic thermal zone; MQGS, mean quartile grading scores; PIH, postinflammatory hyperpigmentation; RCT, randomized clinical trial.

[a]Density (level): Density (level) of the AF CO_2 facility.

[b]Intraindividual: Two facial areas were outlined, marked, and randomized to CO_2 laser treatment versus no treatment.

patients in the Reinholz et al[36] study were treated only on their cheeks. A total of 24 patients' cheeks and 1 patient's nose were treated in the Hsiao et al[20] study. In the Qian et al[19] study, 8 patients had their whole face treated; 9 patients had their cheeks and forehead treated, and 14 patients had only their cheeks treated.

According to the Magnani and Schweiger[16] review, an average energy level of 50 mJ was selected as a cutoff point. Among the 30 studies of this review, 9 studies[19,21–23,28,29,34,35,37] with a total of 208 subjects utilized high energy. Ten studies[20,24–26,30,33,38,42,44,46] with 161 subjects utilized low energy. Unfortunately, we were unable to compare the effects of different energy densities among these studies due to the lack of such information or consistency in reporting energy density levels. However, the effects of high and low energy with the same density of fractional lasers were compared in Kim and Cho's split-face study.[31] At 3 months postoperatively, the mean observers' scores were 5.8 and 4.0, respectively, for the treatment with higher energy and lower energy on a 10-point scale.

Two other articles compared the effects of different fluence and density on the acne scars. In Jung et al's[32] study, the mean grade of clinical improvement was 2.47/4 in the low-fluence, high-density AF CO_2 group—hence lower than the mean grade of 3.37/4 in the high-fluence, low-density AF CO_2 group ($p = 0.02$).[32] Similar results were also found in the Yuan et al study.[33]

The application of AF CO_2 was combined with other treatments in five studies.[31,41–44] The combination of AF CO_2 and NAFR yielded better results than both the high and low energy AF CO_2 groups.[31] Combining AF CO_2 laser and radiofrequency produced better results compared with AF CO_2 monotherapy without increasing the risks or side effects.[41] Applying platelet-rich plasma (PRP) in the AF CO_2-treated areas had a significantly better response than AF CO_2 alone in the Gawdat et al[43] and the Lee et al studies,[44] which was consistent with the results of the Faghihi study.[42] Topical application of adipose-derived stem cells in the Zhou et al study also resulted in increased efficacy of AF CO_2 treatment of atrophic acne scars.[45]

Noninvasive Assessments

Noninvasive and quantitative methods for assessing surface topography have been developed, such as the 3D optical profiling system (Primos 3D),[17,36] Visioscan (VC 98)[29,46] with analysis software, or optical coherence tomography.[43] These techniques generate a high-resolution topographic representation of the acneiform scars pre- and posttreatment, which can then be used to assess the degree of improvement.

Digital photographs were also taken and analyzed using the VISIA Complexion Analysis System to establish the number of pores and follicular openings, as well as atrophic scars and skin texture scores.[20] Reflectance confocal microscopy in Cameli et al's[41] study provided semiquantitative information on the coagulative effects of laser beam treatment.

Compared with the physicians' and patients' evaluation, the imaging technique provides a relatively objective and digitized measurement that is also safer than histology. Moreover, noninvasive quantification of the status of scar and treatment outcomes facilitated in-depth preoperative discussion with patients to set realistic expectations for their treatments.[29]

Adverse Events

In total, 26 out of the 30 studies commented on the adverse effects associated with the fractional CO_2 laser treatment. The most common side effects noted were pain, PIH, erythema and edema, and crusting or scaling. Relative pain scores during the laser treatment were evaluated using 10-cm visual analog scales (VAS).[18,29,30,33–36,38,43,45,46]

Mean VAS pain scores described by the subjects ranged from 2 to 8.16.[29,30] The pain was found to be more evident or persisted for longer periods of time in patients treated with a higher density or higher fluence lasers.[32,33] Walgrave et al[18] found that increased pain scores are correlated with increased density, but not with increased energy of the laser.[18] Average pain scores were found to decline with successive treatment sessions.[29,34]

Postinflammatory hyperpigmentation (PIH) was reported in 19 articles,[17–22,24,28,29,31–35,37–40,46] and tend to resolve spontaneously,[18,19,21,32,33,35] or can be successfully treated with antipigmentation cream.[18,24,28,29,38,46] Most of the PIH cases resolved within 3 months (by the follow-up appointment).

Compared with the multiple-pass approach, the single-pass technique for the delivery of the same total density was more likely to develop PIH,[19] which is consistent with the fact that PIH were found to be more evident or persisted for longer periods of time in patients treated with higher densities or higher fluences.[33] PIH appears to be more related to the density rather than the energy of the laser treatment. Based on the low incidence of PIH, Hsiao et al[20] considered a density of 10 to 15% to be safe.

Erythema was graded after each treatment session using several different scales, including a 5-point scale,[44,45] a 0 to 10 VAS system,[42] or a numerical scale from 0 to 3.[17,18,30,33,34] Mild-to-moderate erythema (lasting an average of 2.87 days) was reported immediately after all three treatment sessions in the Cho et al study.[21] According to patients' self-evaluations in the Kim et al study,[25] it can be present for up to approximately 1 month. Erythema was found to be more evident or persisted for longer periods of time in patients treated with higher densities or higher fluences of the laser.[33] In general, mild to moderate edema was noted in the treatment area in all subjects and resolved within 1 week in most studies.

Mean duration of posttherapy crusting or scaling was approximately 7 days according to patients' account. Mean duration of limited daily activities, such as going outdoors or working was 4.9 ± 2.1 days. This was found to correlate significantly with the appearance of posttherapy crusting or scaling but not with posttherapy erythema.[21]

Other adverse effects included herpes reactivation, oozing, bleeding, petechiae, stinging sensation, cutaneous pruritus, and allergic contact dermatitis.[20–22,28,29,33,39,40] No permanent side effects were reported.

Discussion

Acne scarring results after deviation from the usual repair of the skin during the acne healing process. The high ratio of Asian participants in the reviewed articles was partly due to the high prevalence of acne in Asian populations. According to Lynn's review,[48] Taiwan (East Asia) and South Asian countries have the highest worldwide prevalence of acne among their late adolescence (range: 15–19 years) age groups. This finding was consistent with Ghodsi et al's[49] review of several large worldwide studies on the prevalence of acne vulgaris among adolescent age groups. It can be assumed that this subpopulation of acne patients has serious concerns about their appearance.

The direct association between inflammatory acne lesions and the severity of scarring indicates that the most effective means of addressing acne scarring is to prevent its formation through good acne control.[50] In fact, patients enrolled in the reviewed studies often had active acne or were under concurrent acne therapy. However, treatment of the scars was often delayed because of the current recommendation that acne scar revision is performed no sooner than 6 to 12 months[51] or even 12 to 24 months[49] after completion of oral isotretinoin treatment.

It is assumed that retinoids can delay or alter reepithelialization,[52] although the role of retinoids in wound healing is debatable and controversial. Evidence shows that topical application of tretinoin to the wound of adult model animals increases collagen synthesis in aged skin and promotes the normal skin healing process.[53]

In Yoon et al's[54] study, isotretinoin (10 mg/d) was also confirmed to be a safe and effective treatment for acne and acne scars when combined with fractional laser therapy. Likewise, 10 to 40 mg/d isotretinoin was used simultaneously with AF CO_2 in Kim and Cho's[25] study, and the findings suggest that ablative fractional laser treatment for acne scars is safe regardless of isotretinoin use at accumulated dose of 39 to 248 mg/kg. Considering that acne scar treatment is a lengthy process and requires a combination of procedures, early initiation of treatment could greatly improve the quality of life of patients.

We recommend that isotretinoin should be used for patients with moderate-to-severe acne during both the pre- and postoperative period except for patients undergoing immune suppression or those with contraindications such as diabetes.

Ablative laser therapy has been linked to damaged skin barriers (dryness), accelerated inflammatory reaction in the form of acneiform eruption or herpes simplex infections, as well as high risk of PIH. Traditionally, application of pharmaceuticals, such as steroids, antivirals, antibiotics, and antipigments, such as hydroquinone is a standard protocol to address these issues. Recently, the use of dermocosmetics has been demonstrated to improve acne, dry skin, and hyperpigmentation effectively.[55–57] Therefore, dermocosmetics have the potential to be used as a monotherapy or in combination with medical treatments for postoperative skin care.

In theory, a single treatment for atrophic acne scars is always beneficial as it can ensure high patient compliance, avoid repetition of scabbing, and minimize postoperative sick leave from work that is often taken after every treatment session. However, acne scar treatments are often a continuous process rather than a one-time intervention. When multiple treatments are required to achieve preferred long-term results, an approximate 3-month interval between treatment sessions appears to be optimal.

A shorter interval may reduce the maximum wound-healing response achievable from the previous session,[58] cause excessive transepidermal water loss, and compromise the recovery of the melanin–erythematic index.[58] On the other hand, longer intervals could be less effective as the next treatment has a greater tendency of injuring the tissues that are being replaced. Indeed, it has been shown that the more collagen is rebuilt from the previous treatment, the more damage is likely to be caused by the subsequent treatment.[34]

The treatment options for acne scars should be tailored for each patient. First, the treatment protocol should take into account the clinical features of the scar characteristics (depth, width, and type). Certain types of acne scarring may respond more favorably to AF CO_2 laser treatment. According to several studies, boxcar and superficial atrophic scars respond better than deeper scars.[18,19] The ice-pick scar, which is usually deep and sharp, may not be a good candidate for this approach.[22,28]

The current recommendation for ice-pick scars calls for skin punch excision or chemical reconstruction techniques.[8] However, additional options are available to resolve this condition, such as filler injections, PRP (intradermal or topical), and radiofrequency combination therapy.

Second, when AF CO_2 laser is applied to the entire face, parameters (energies and passes) should be modulated to different regions of the face. Maximum energies can be used for the primary acne scar target areas, and most passes can be delivered to the neck, chin, lips, cheeks, and forehead. Aggressive treatment (with high fluences and multiple passes) should be avoided in sensitive areas, such as the neck and the eyelids to reduce the risk of complications.[26] Skin thickness should also be considered. According to a recent study, the treatment appeared to be more effective in younger patients with thinner skin.[59] Sebaceous skin is usually thicker,[39] and thus may necessitate increased number of passes, as well as a higher power of fluence and treatment density. It is therefore advisable that physicians use variable parameters for the same patient according to the assessment of the conditions.[39]

Third, treatment parameters can vary between the sessions —for example, treatment coverage can increase throughout the treatment series. It has been observed that treatments became more tolerable and the recovery became increasingly faster and better throughout the treatment series.[17] It is also important that when the safety and effectiveness of the device are established for a specific patient throughout the course of treatment, the investigator can often become more confident with the device and outcome.[18]

Conclusion

The fractional carbon dioxide laser is an effective therapy for the treatment of acne scars. It is imperative to consider the characteristics of the scar (such as main complaint, type, severity, history, and prior and ongoing treatments), design individualized treatment plans (such as parameters, intervals, monotherapy or combination therapy, and means of anesthesia), and communicate details of the treatment outcome (such as results, budget, schedule, and pain-bearing) so that physicians can achieve optimum results and a timeframe that meets the patient's informed expectations.

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