AUTHOR QUERIES

DATE 5/11/2018
JOB NAME DS

ARTICLE DS-00611-2017
QUERIES FOR AUTHORS Moftah et al

THIS QUERY FORM MUST BE RETURNED WITH ALL PROOFS FOR CORRECTIONS

Please confirm the given names (pink) and surnames (blue) of authors have been identified correctly.

AU1) Please check the minor edit made to the article title.
AU2) Please check whether all forenames and surnames have been identified correctly.
AU3) Please provide the Department/Unit (if any) in affiliation "†."
AU4) Please note that as per style the second e-mail address has been deleted as only one e-mail address can be retained.
AU5) Please confirm the conflict of interest statement.
AU6) Please note that as per style, the abstract sub headings should be "BACKGROUND, OBJECTIVE, PATIENTS AND METHODS/MATERIALS AND METHODS/METHODS, RESULTS, AND CONCLUSION." Please check and change if necessary.
AU7) Please provide manufacturer city for the manufacturer "LEO Mina Pharm."
AU8) Please provide the year of publication for the reference 3.
AU9) Please check the layout of Table 2.

Carboxytherapy Versus Skin Microneedling in Treatment of Atrophic Postacne Scars: A Comparative Clinical, Histopathological, and Histometrical Study

Noha H. Moftah, MD,* Mohammad A.M. El Khayyat, MD,* Maha H. Ragai, MD,* and Heba Alaa, Msc†

BACKGROUNDS Acne scarring has been a challenge to treat. Microneedling gained popularity in treatment of such scars. Meanwhile, carboxytherapy (CXT) is considered a novel treatment modality for acne scars.

OBJECTIVE To evaluate efficacy of CXT versus microneedling in treatment of acne scars.

METHODS AND MATERIALS Thirty-two patients with atrophic acne scars received 6 sessions of microneedling and CXT on right and left sides of face, respectively. Clinical evaluation with histopathological and computerized morphometric analysis was performed at 2 months after treatment.

RESULTS After either microneedling or CXT, there was significant decrease of total acne scars and its 3 types separately (icepicks, boxcar, and rolling) ($p \leq .001$). Comparing both sides of face, there was no significant difference regarding grading response and reduction percentage of total scars and its types ($p > .05$). Histopathologically, there was an improvement of character and organization of collagen and elastic fibers in addition to significant increase in epidermal thickness on both sides of face, with no significant difference between them ($p > .05$).

CONCLUSION Both CXT and microneedling are equally effective, tolerable, safe, and noninvasive treatment modalities of atrophic acne scars. Similar histopathological changes were observed after both modalities, helping in better understanding their action.

The authors have indicated no significant interest with commercial supporters.

Acne vulgaris is a common skin disorder of pilosebaceous unit, and it causes scar formation that leads to psychologically disturbing condition.[1] The rate of acne scarring ranged from 1% to 11%[2] and up to 90% of patients with acne.[3]

Eighty to 90% of patients of acne scars have atrophic type,[4] which may be related to inflammatory mediators and enzymatic degradation of collagen fibers.[3] These atrophic acne scars have been divided into 3 types including icepicks, boxcar, and rolling.[1]

Various therapeutic options have been described in treatment of atrophic postacne scars including microneedling, microdermabrasion, laser (ablative, nonablative, or fractional), dermabrasion, autologous fat transfer, injection of dermal fillers, and surgical methods.[5]

The ablative laser resurfacing and dermabrasion, that offer significant improvement in facial scars, are invariably associated with considerable morbidity and long downtime.[6] On the other hand, nonablative laser resurfacing and microdermabrasion, that are associated with a minimal downtime, do not show the same efficacy as ablative resurfacing techniques.[6,7] Moreover, fractional laser resurfacing has been reported to allow for recontouring of scars; however,

*Department of Dermatology, STD's and Andrology, Faculty of Medicine, Minia University, Al Minya, Egypt; †Dermatology and Leprosy Hospital, Al Minya, Egypt

ISSN: 1076-0512 • Dermatol Surg 2018;00:1–10 • DOI: 10.1097/DSS.0000000000001560

postinflammatory hyperpigmentation in patients with darker skin types often preclude sufficient treatment.[8]

Microneedling or percutaneous collagen induction therapy is considered the most effective, noninvasive, inexpensive, and popular treatment modality for atrophic postacne scars all over the world with minimal downtime,[9–11] especially in patients with Fitzpatrick's IV and V skin types.[12]

There are many devices used for microneedling in the market such as fixed needle rollers and automated or electric-powered pen devices with disposable sterile needle tips.[13–15] These devices vary based on the needle length, quantity, diameter, configuration, and material. Meanwhile, the automated pen device offers several advantages over roller drum devices such as easy adjustment of its operating speeds and penetration depths (from 0.5 to 2.5 mm) during the same session resulting in efficient treatment of either large or small surface areas.[14,15]

Carbon dioxide (CO_2) therapy, commonly known as carboxytherapy (CXT), refers to cutaneous and subcutaneous administration of CO_2 gas.[16] In the tissue, CO_2 reacts with water molecules resulting in molecular carbonic acid, which reduces the tissue pH. Here, the Bohr effect comes into play (the lower the pH, the weaker the bond between hemoglobin and oxygen), leading to release of oxygen from hemoglobin and vasodilatation of microcirculation accompanied by an increase of peripheral blood flow.[16,17] Moreover, Ferreira and colleagues[18] described an increase in collagen remodeling induced by intradermal injections of CO_2.

The technique of CXT is increased in popularity in the field of aesthetics and particularly for dermal rejuvenation and fat lipolysis. Accordingly, it is most efficacious in treatment of periorbital dark halos, wrinkles, burns, wound healing, stretch marks, cellulite,[16] and surgical scars.[19] Meanwhile, CXT is considered an uncommon addition to treatment modalities for atrophic postacne scars, and there were no studies evaluating objectively its clinical and histopathological effects in such scars.

This study aimed to evaluate the clinical and histopathological efficacy of CXT versus skin microneedling in treatment of atrophic postacne scars.

Methods

Patients

This study included 32 patients, with facial atrophic postacne scars, who were collected from Dermatology Out-patient Clinic of Minia University Hospital. An informed written consent was taken from each patient, and the study was approved by Committee for Postgraduate Studies and Research of Faculty of Medicine, Minia University. Complete general and dermatological examinations were performed.

Patients with some dermatological disorders (active acne, eczema, psoriasis, warts, recurrent herpes infection, or keloidal tendency) and chronic medical diseases (respiratory, renal, heart or liver failure, anemia, or gaseous gangrene) were excluded from the study. Moreover, this study did not include patients using topical formulations (taken within previous 1 month), systemic drugs, and laser- or light-based therapy (used within previous 6 months).

Treatment Protocol and Postoperative Care

This study performed 6 sessions of microneedling and CXT on right and left sides of the face, respectively, with 2-week interval.

Skin Microneedling

On the right side of face, 2.5% lidocaine/prilocaine anesthetic cream (Emla cream; AstraZeneca AB, Södertälje, Sweden) was applied to the treated areas under occlusion 1 hour before microneedling. After disinfection with 70% alcohol, microneedling was performed using automated microneedling device (Genuine Dermapen; Dermapenworld Equipmed company, Terry Hills, New South Wales, Australia), with adjustable needle length of 2 mm. This device consists of electric hand piece and a disposable needle tip, containing 36 microscopic needles. The skin area to be treated was rolled in 4 different directions (horizontally, vertically, and diagonally right and left) with stretching the skin in a perpendicular direction to microneedling movement to reach base of scars. The end point was appearance of erythema with pinpoint bleeding, which disappeared immediately by pressure with wet saline gauze.

Carboxytherapy

The left side of face was treated with CXT using carboxy-pen (Concerto, CP amm-0000, CE 0459; BFP Electronique, Le Vimenet, France), which was connected to CO_2 cylinder. After disinfection with 70% alcohol, an intradermal injection of 3 cc of CO_2 was performed using 30-gauge needle at 5-mm interval, 2-mm depth, and an angle of 15°. The injected area appeared white, then, erythematous with discrete increase of volume because of spread of the gas for at least 5 mm. So, the total number of injections ranged from 5 to 8 per the entire cheek. Then, gentle massage was performed.

Postoperative Car

Fusidic Acid 2 mg (Fusidin ointment; LEO Mina Pharm, AQ : 7 Egypt) was applied to guard against secondary bacterial infection for 24 hours. Then, moisturizing cream was applied until resolving of the erythema. Sunscreen with sun protection factor ≥50 was recommended in between sessions and 2 months after treatment.

Clinical Evaluation

Grading of Acne Scars

At baseline and 2 months after last session, both sides of face were photographed and assessed clinically through grading the severity of atrophic scarring according to Goodman and Baron.[20] The grading of scars after treatment was then compared with that in the pretreatment period.[21] If change in the grade of severity after treatment was reduction of 2 grades or more, the improvement was labeled as excellent response, whereas a good response meant an improvement by 1 grade only. Moreover, the improvement was considered poor if there was no reduction in grade of scarring.

Count of Acne Scars

An objective blinded method for evaluation was performed by counting each type of scar (icepicks, boxcar, and rolling) with determination of total number of all types[22] in all patients at baseline and 2 months after treatment. Then, reduction percentage was calculated. The patients were asked about any side effects noticed every session and at 2 months after treatment.

Skin Biopsy

Skin biopsy specimens were obtained, using 2-mm punch probes, from both sides of the face of 16 patients at baseline and 2 months after last session from the nearest point to baseline. Each biopsy was immediately fixed in 10% formalin, embedded in a paraffin block, and sectioned into 5-μm thick sections. These sections were subjected to histopathological examination using hematoxylin and eosin (H&E), Masson trichrome (for collagen fibers) and orcein stains (for elastic fibers). Light microscope (Accu-Scope # 3025 5 headed [A3025-5]-Olympus, Tokyo, Japan) with a built-in camera (digital camera E-330 SLR; Olympus, Tokyo, Japan) was used to examine the sections by 2 blinded histopathologists and photograph them.

Morphometric Measurement of Epidermal Thickness

The epidermal thickness was determined in H&E-stained sections of 16 patients, using a computer-based software (analysis Five by Olympus Soft imaging solutions GmbH, Johann-Krane-Weg 39, D-48149 Münster, Germany). Five measurements for each section were calculated between top of granular cell layer to dermoepidermal junction with calculation of mean value.[11]

Statistical Analysis

Data were statistically analyzed using SPSS for Windows (Version 16.0.1; SPSS, Inc., Chicago, IL). Quantitative data were expressed as range and mean ± SD, whereas qualitative data were expressed as number and percent. Statistical analysis included paired *t*-test, independent student *t*-test, and analysis of variance test for quantitative data and chi-square for qualitative data. Significance was expressed in terms of *p* value, which was considered significant when it was ≤.05.

Results

This study included 32 patients with facial atrophic acne scars (10 men [31.25%] and 22 women [68.75%]). Their ages ranged from from 18 to 40 years, with a mean of 26.3 ± 7.17 years. Regarding Fitzpatrick skin typing, 4 (12.50%), 14 (43.75%), and 14 patients (43.75%) had skin Type II, III, and IV, respectively.

Clinical Results

Grading of Acne Scars

At baseline, Grade II was evident in 4 patients (12.5%), Grade III in 20 patients (62.5%), and Grade IV in 8 patients (25%). After microneedling, excellent, good, and poor response was achieved in 18 (56.25%), 12 (37.5%), and 2 (6.25%), respectively. Meanwhile, left side of the face, treated by CXT, [F1] showed excellent, good, and poor response in 14 [F2] (43.75%), 14 (43.75%), and 4 (12.5%), respectively, with no significant difference between 2 sides of the [T1] face ($p > .05$) (Figures 1 and 2 and Table 1).

Count of Acne Scars

After either skin microneedling or CXT, there was significant decrease of count of total scars and its 3 types separately ($p \leq .001$). Comparing both sides of the face, there was no significant difference in the count of icepicks, boxcar, rolling, and total scars either before ($p = .9$, $p = .8$, $p = .2$, $p = .7$, respectively) or after treatment ($p = .8$, $p = .4$, $p = .3$, $p = .7$, respectively) (Figures 1 and 2 and Table 2). [T2]

Percentage of Reduction of Postacne Scars

After microneedling, the mean percentages of reduction of total, icepicks, boxcar, and rolling acne scars were 60.68%, 59.71%, 50.85%, and 57.69%, respectively, with no significant difference between 3 types of acne scars ($p > .05$). After CXT, the mean percentages of reduction of total acne scars, icepicks, boxcar, and rolling scars were 61.62%, 64.62%, 48.01%, and 55.93%, respectively, with no significant difference among 3 types of acne scars ($p > .05$). Comparing both sides of the face, there was no significant difference in reduction percentage of total

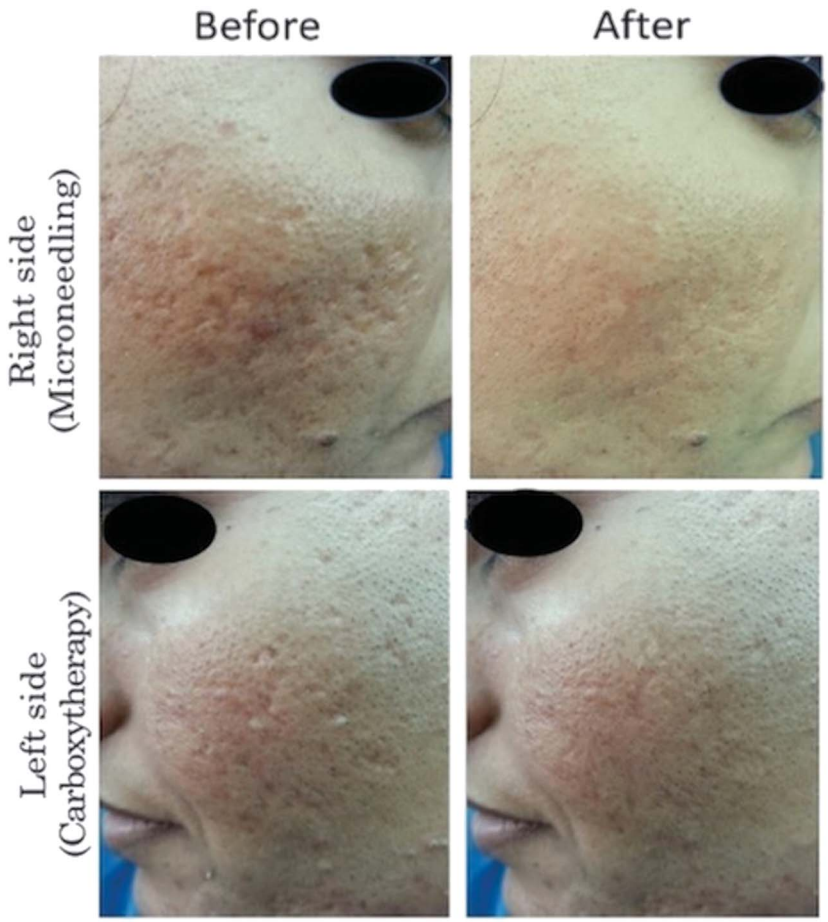

Figure 1. Female patient with postacne scars before and after treatment. Both right (microneedling) and left sides of the face (carboxytherapy) show excellent improvement after both methods of treatment.

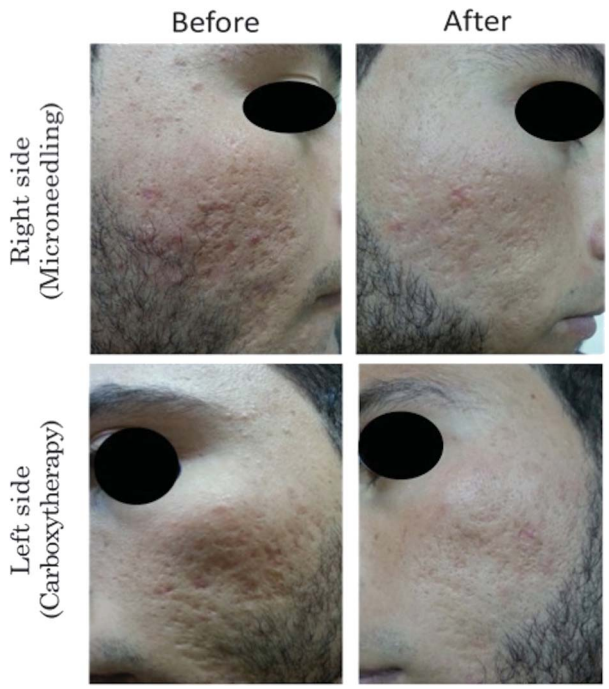

Figure 2. Male patient with postacne scars before and after treatment. Right side of the face (microneedling) showing good response; however, left side of the face (carboxytherapy) has excellent improvement.

scars (p = .7) and its 3 types separately (icepicks [p = .1], boxcar [p = .8], and rolling scars [p = .7]) (Table 2).

Safety and Tolerability

After each microneedling session, there were erythema and edema, which resolved within 1 to 2 days after session. Meanwhile, patients reported transient erythema, warmness, and swelling of the area injected after each CXT session, resolving within 10 minutes to 1 hour later. During either microneedling or CXT, there was mild tolerable pain, which subsided shortly after session in all patients. At 2 months after last session of microneedling or CXT, there were no side effects detected.

Histopathological Results

Collagen Fibers (Masson Trichrome Stain)

At baseline, the collagen fibers were disorganized with increased interfibrillary spaces in right and left sides of face (in 14 [87.5%] and 13 patients [81.3%], respectively), with no significant difference between them (p = .10). After treatment, the collagen fibers became fine, dense, and well-organized in normal lattice pattern with decreased interfibrillary spaces in right and left sides of face (in 12 [75%] and 13 patients [81.3%], respectively), with no significant difference between them (p = .09). There was significant increase in the number of biopsies showing improvement of collagen character and organization after either microneedling (p = .02) or CXT (p = .01), compared with baseline (Figure 3). [F3]

Elastic Fibers (Orcein Stain)

Before treatment, abnormal dense elastic tissue was demonstrated in close contact with epidermis in right and left sides of face (in 13 [81.3%] and 14 patients [87.5%], respectively), with no significant difference between them (p = .16). Meanwhile, post-treated biopsies of right and left sides of face (in 14 [87.5%] and 15 patients [93.8%], respectively) showed reduction of density of elastic tissue that moved downward with appearance of fine and well-organized newly synthesized elastic fibers, with no significant difference between both sides of the face (p = .09). There was significant increase in the number of biopsies showing improvement of elastic fiber character and organization after either microneedling (p = .01) or CXT (p = .03), compared with baseline (Figure 4). [F4]

Morphometric Results of Epidermal Thickness

After microneedling, the epidermal thickness was significantly increased ([range, 69.4–97.7 μm]; [mean,

TABLE 1. Grading of Improvement of Acne Scars After Therapy on Both Sides of the Face

Grading	*Right Side (Microneedling), (n = 32)*	*Light Side (Carboxytherapy), (n = 32)*	*p*
Excellent	18 (56.25%)	14 (43.75%)	.454
Good	12 (37.5%)	14 (43.75%)	.799
Poor	2 (6.25)	4 (12.5)	.672

AQ : 9

TABLE 2. Comparison of Count of Acne Scars on Both Sides of the Face Before and After Therapy With Their Reduction Percentages After Treatment

	Right Side (n = 32)			*Left Side (n = 32)*		
Acne Scars	*Before*	*After*	*P*	*Before*	*After*	*P*
Total acne scars						
Count						
Range	20–75	6–39	<0.001	23–63	9–28	<.001
Mean ± SD	48.94 ± 13.93	19.63 ± 7.57		47.38 ± 12.53	18.31 ± 6.25	
Reduction percentage (%)						
Range		48–72.13			47.83–72.5	
Mean ± SD		60.68 ± 6.75			61.62 ± 6.86	
P1			.7			
Icepick						
Count						
Range	12–50	4–28	<0.001	5–39	2–19	<.001
Mean ± SD	31.31 ± 10.95	13.06 ± 6.57		27.94 ± 10.38	9.94 ± 4.45	
Reduction percentage (%)						
Range		44–80			50–74.36	
Mean ± SD		59.71 ± 9.49			64.62 ± 6.75	
P1			.1			
Boxcar						
Count						
Range	0–9	0–3	0.001	0–7	0–2	.001
Mean ± SD	3.13 ± 3.12	1 ± 1.15		2.75 ± 2.21	0.94 ± 0.85	
Reduction percentage (%)						
Range		0–100			0–100	
Mean ± SD		50.85 ± 38.35			48.01 ± 36.77	
P1			0.8			
Rolling						
Count						
Range	0–25	0–9	<0.001	5–40	2–21	<.001
Mean ± SD	14.5 ± 6.27	5.56 ± 2.42		16.69 ± 8.49	7.44 ± 4.53	
Reduction percentage (%)						
Range		0–75			40–73.33	
Mean ± SD		57.69 ± 16.37			55.93 ± 8.82	
P1			0.7			

P; *p* value of acne scar counts between before and after treatment on each side of the face.
P1; *p* value between reduction percentage of right and left sides of the face.

75.79 ± 7.64 μm]), when compared with baseline ([range, 55.1–77.4 μm]; [mean, 62.06 ± 5.45 μm]; [$p < .001$]). Moreover, the left side of the face (CXT) showed significant increase in the epidermal thickness ([range, 68.1–103.7 μm]; [mean, 78.59 ± 12.29 μm]), when compared with baseline ([range, 54.8–78.1 μm]; [mean, 62.54 ± 5.15 μm]; [$p = .002$]). On comparing both sides of the face, there was no significant difference in the epidermal thickness either before ($p = .17$) or after treatment ($p = .20$) (Figure 5). [F5]

Discussion

Atrophic postacne scar is one of the most dramatic consequences after inflammatory acne. There are different treatment options for such scars; however, most of them showed minimal clinical efficacy or considerable morbidity and long downtime.[21] So, other minimally invasive techniques are used for treatment of acne scars to overcome these limitations. Many studies, concerning the efficacy of microneedling, have been published;[9–11]

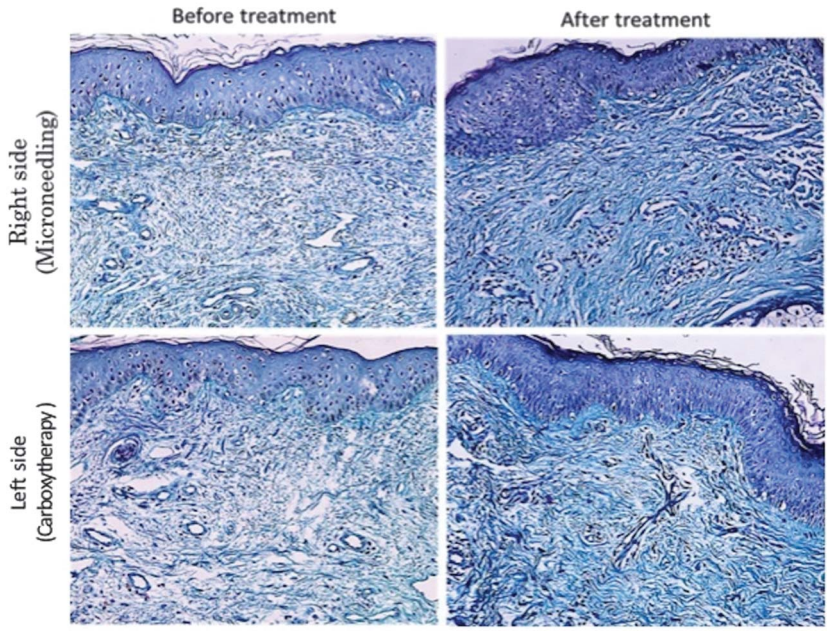

Figure 3. Postacne scars biopsies before and after treatment in right and left sides of the face. Pretreated biopsies showing disorganized collagen bundles with increased interfibrillary spaces in both sides of the face. After treatment, post-treated biopsies demonstrate more-dense collagen fibers, which become fine and well-organized in a normal lattice pattern with darker stain and decreased interfibrillary spaces on both sides of the face (Masson trichrome, ×200).

however, CXT is considered uncommon addition to the treatment modalities for acne scars. Accordingly, this study aimed to evaluate clinical and histopathological efficacy of CXT versus skin microneedling in treatment of atrophic postacne scars.

After microneedling, objective counting of total acne lesions after microneedling showed significant decrease in the number of total postacne scars with reduction percentage of 60.68%. This agrees with Leheta and colleagues,[10] who reported 68.3% overall

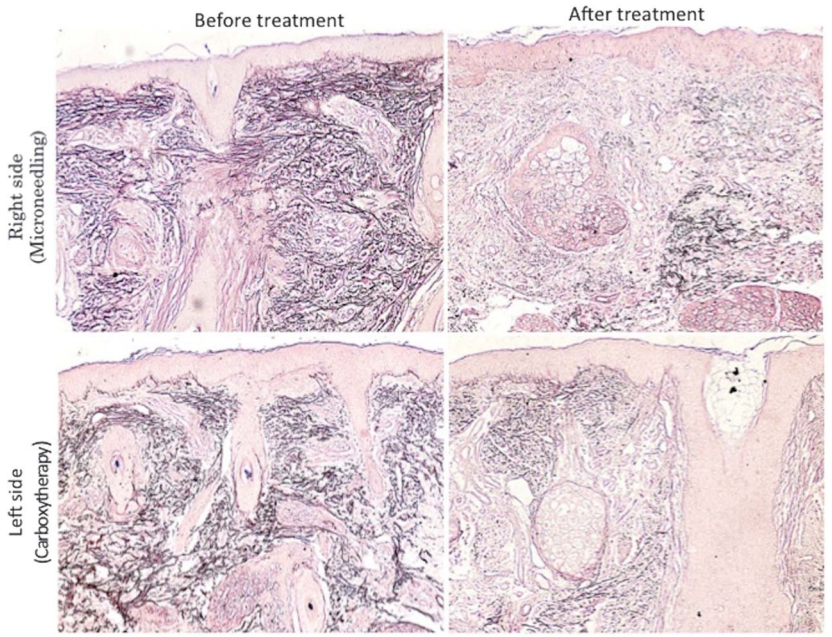

Figure 4. Postacne scars biopsies before and after treatment in right and left sides of the face. Pretreated biopsies showing abnormal dense elastic tissue in close contact with epidermis in both sides of the face. After treatment, post-treated biopsies demonstrate less-dense elastic tissue that moved downward in the dermis with the appearance of newly synthesized elastic fibers, which are fine and well-organized (Orcein, ×100).

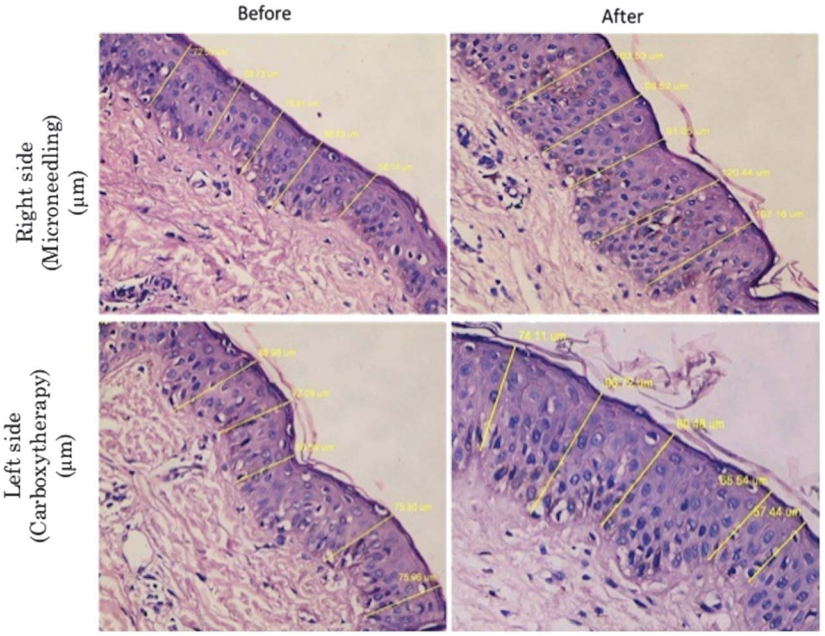

Figure 5. Histometry of postacne scars biopsies showing significant increase in the epidermal thickness on both sides of the face after both treatment modalities when compared with pretreated biopsies of acne scar patients (H&E, ×400).

scar improvement. By grading clinical response, excellent, good, and poor response was detected in 56.25%, 37.50%, and 6.25% of patients, respectively. This is quite similar to many microneedling studies, which showed that the severity of the acne scars was significantly reduced in all patients, varying from good response in most patients[11,23] reaching to excellent response in 72.2% of patients.[21]

In the subset analysis of types of atrophic scars, there was significant decrease in the number of 3 types of acne scars after microneedling in the following order: icepick, rolling, and boxcar, but with no statistically significant difference between them. Meanwhile, other studies reported good to excellent response in rolling[9–11,21] and boxcar scars, and moderate response in icepick scars.[11,21]

Regarding CXT, the left side of the face had excellent, good, and poor response in 43.75%, 43.75%, and 12.50% of patients, respectively. Moreover, counting technique revealed significant decrease in total atrophic scars with reduction percentage of 61.62%. Regarding types of acne scars, there was significant decrease in their number in the following order: icepick, rolling, and boxcar, but with no statistically significant difference between them. On reviewing literature, there were no studies using CXT for treatment of atrophic acne scars; however, there was only one case report that performed CXT for treatment of rhytidectomy scar, and significant improvement was observed with a great advance.[19]

On comparing CXT and microneedling, there was no significant difference between 2 sides of face regarding improvement of grading stages and reduction percentage of total acne scars and its 3 types.

After each session of microneedling, patients reported transient erythema and edema, which resolved 1 to 2 days later. There are consistent with the previous studies.[9–11,21] Meanwhile, after each session of CXT, patients reported transient erythema, warmness, and swelling of the area injected, which resolved after 10 minutes to 1 hour later. This is consistent with Nach and colleagues.[19]

Generally, the epidermis is considered the first layer of protection from the environment.[24] Accordingly, there was no risk of photosensitivity and postinflammatory hyperpigmentation at 2 months after last session since the epidermis remains intact after either microneedling[11,25] or CXT.[16]

By quantitative evaluation of the epidermis, there was significant increase in the epidermal thickness on both sides of face after 2 treatment modalities, with no

significant difference between them. This result is similar to the objective microneedling study of El Domyati and colleagues[11] Meanwhile, there were no studies evaluating CXT on epidermal thickness.

In the dermis, collagen fibers form a network with elastic fibers resulting in a highly ordered structure. Meanwhile, collagen is considered the main structural and most abundant extracellular matrix component of dermis, playing an essential role for strength and elasticity of healthy skin and scar tissue.[26] By contrast, elastic fibers compose 1% to 2% of dermis, and they are critical to the ability of skin to stretch and recoil.[27]

In this study, there was significant improvement of collagen fibers, which became fine, dense, and well-organized in a normal lattice pattern after both treatment modalities, with no significant difference between them. This agrees with many microneedling studies on atrophic postacne scars.[9,11,25] Regarding CXT, there were no studies evaluating its histopathological effect on atrophic acne scars. However, Brandi and colleagues[28] observed thick dermis with diffusely distributed collagen fibers after CXT for treatment of localized adipocytes. Moreover, an animal study showed that injection of CO_2 gas leads to increased collagen turnover with more arrangement in the dermis, simulating the dermis of young animals.[24]

Regarding elastic fibers, this study revealed significant improvement in quality and distribution of elastic tissues, with appearance of fine and well-organized newly synthesized elastic fibers after both microneedling and CXT, with no significant difference between them. This is similar to many microneedling studies.[11,25] Regarding CXT, the only study, reporting significant increase in normal fine elastic fibers, compared CXT versus radiofrequency on skin rejuvenation.[29] Moreover, Brandi and colleagues[28] observed improvement of elasticity, which was measured by cutometer after CXT for treatment of localized adipocytes.

Surprisingly, it seems that both microneedling and CXT acts through dermal remolding and increase in epidermal thickness, but with different theories. Regarding CXT, one hypothesis concerns that it improves oxygenation by increased liberation of oxygen based on Bohr's effect (in lower pH and higher pCO_2, the affinity of hemoglobin to oxygen is decreased)[16,17] accompanied with vasodilatation through relaxation of the prearteriolar smooth muscle and opening of precapillary sphincters leading to increase in the blood flow velocity and tissue perfusion.[30] The other theory suggested that tissue stretching during infusion induces a subclinical inflammation, which triggers repair and tissue regeneration that induce activation of macrophages, fibroblasts, and endothelial cells that stimulate neovascularization and remodeling of the extracellular matrix.[31] Moreover, the mechanical stretching and pressure on dermal fibroblasts and keratinocytes leads to their proliferation and differentiation[32] with release of cytokines and growth factors of autocrine and paracrine effects by fibroblasts.[33]

On the other hand, the main mechanism hypothesized for the action of microneedling is that it creates thousands of microclefts of superficial injury and bleeding through the epidermis into papillary dermis, releasing growth factors and initiating the normal process of wound healing with its 3 consecutive stages that lead to increase in collagen production and tightening with subsequent improvement of scar appearance.[11,25] The other hypothesis concerns breaking of old collagen strands that connect the scar with the upper dermis by needles, where removal of damaged collagen and neocollagenesis occur.[24]

In conclusion, both CXT and microneedling are simple, tolerable, safe, and noninvasive treatment modalities of atrophic postacne scars with comparable efficacy and low downtime. Moreover, similar histopathological changes occurred after both treatment modalities such as improvement of character and organization of collagen fibers and rectification of elastic fibers degeneration in addition to increased epidermal thickness. Accordingly, these similar results could help in better understanding their mechanism of action.

References

1. Jacob CI, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. J Am Acad Dermatol 2001;45:109–17.

2. Goodman GJ. Postacne scarring: a review of its pathophysiology and treatment. Dermatol Surg 2000;26:857–71.

3. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol;194:303–8.

4. Shraddhamayananda S. An observation successful treatment of acne scar with homeopathic medicine. Int J Biopharmaceutics 2015;6:27–31.

5. Kim HJ, Kim TG, Kwon YS, Park JM, et al. Comparison of a 1,550 nm Erbium: glass fractional laser and a chemical reconstruction of skin scars (CROSS) method in the treatment of acne scars: a simultaneous split-face trial. Lasers Surg Med 2009;41:545–9.

6. Alster TS, Lupton JR. An overview of cutaneous laser resurfacing. Clin Plast Surg 2001;28:37–52.

7. Shim EK, Barnette D, Hughes K, Greenway HT. Microdermabrasion: a clinical and histopathologic study. Dermatol Surg 2001;27:524–30.

8. Chan HH, Manstein D, Yu CS, Shek S, et al. The prevalence and risk factors of post-inflammatory hyperpigmentation after fractional resurfacing in Asians. Lasers Surg Med 2007;39:381–5.

9. Fabbrocini G, Fardella N, Monfrecola A, Proietti I, et al. Acne scarring treatment using skin needling. Clin Exp Dermatol 2009;34:874–9.

10. Leheta T, El Tawdy A, Abdel Hay R, Farid S. Percutaneous collagen induction versus full-concentration trichloroacetic acid in the treatment of atrophic acne scars. Dermatol Surg 2011;37:207–16.

11. El-Domyati M, Barakat M, Awad S, Medhat W et al. Microneedling therapy for atrophic acne scars: an objective evaluation. J Clin Aesthet Dermatol 2015;8:36–42.

12. Singh A, Yadav S. Microneedling: advances and widening horizons. Indian Dermatol Online J 2016;7:244–54.

13. Doddaballapur S. Microneedling with dermaroller. J Cutan Aesthet Surg 2009;2:110–1.

14. Arora S, Gupta PB. Automated microneedling device—a new tool in dermatologist's kit—a review. J Pakistan Assoc Dermatologists 2012; 22:354–7.

15. Alster TS, Graham PM. Microneedling review a, guide practical. Dermatol Surg 2017;0:1–8.

16. Zenker S. Carboxytherapy, carbon dioxide injections in asthetic medicine. Prime J 2012;2:42–50.

17. Hartmann BR, Bassenge E, Pittler M. Effect of carbon dioxide-enriched water and fresh water on the cutaneous microcirculation and oxygen tension in the skin of the foot. Angiology 1997;48:337–43.

18. Ferreira JCT, Haddad A, Tavares SA. Increase in collagen turnover induced by intradermal injection of carbon dioxide in rats. J Drugs Dermatol 2008;7:201–6.

19. Nach R, Zandifar H, Gupta R, Hamilton JS. Subcutaneous carboxytherapy injection for aesthetic improvement of scars. Ear Nose Throat J 2010;89:64–9.

20. Goodman GJ, Baron JA. Postacne scarring—a quantitative global scarring grading system. J Cosmet Dermatol 2006;5:48–52.

21. Majid I. Microneedling therapy in atrophic facial scars: an objective assessment. J Cutan Aesthet Surg 2009;2:26–30.

22. Bhardwaj D, Khunger N. An assessment of the efficacy and safety of CROSS technique with 100% TCA in the management of ice pick acne scars. J Cutan Aesthet Surg 2010;3:93–6.

23. Dogra S, Yadav S, Sarangal R. Microneedling for acne scars in Asian skin type: an effective low cost treatment modality. J Cosmet Dermatol 2014;13:180–7.

24. Fernandes D, Signorini M. Combating photoaging with percutaneous collagen induction. Clin Dermatol 2008;26:192–9.

25. Aust MC, Fernandes D, Kolokythas P, Kaplan HM et al. Percutaneous collagen induction therapy: an alternative treatment for scars, wrinkles and skin laxity. Plast Reconstr Surg 2008;121:1421–9.

26. Bernstein EF, Andersen D, Zelickson BD. Laser resurfacing for dermal photoaging. Clin Plast Surg 2000;27:221–40.

27. Uitto J, Olsen DR, Fazio MJ. Extracellular matrix of the skin: 50 years of progress. J Invest Dermatol 1989;92:61S–77S.

28. Brandi C, D'Aniello C, Grimaldi L, Bosi B et al. Carbon dioxide therapy in the treatment of localised adiposities: clinical study and histopathological correlations. Aesthet Plast Surg 2001;25:170–4.

29. Pinheiro NM, Crema VO, Millan BM, Carvalho FA et al. Comparison of the effects of carboxytherapy and radiofrequency on skin rejuvenation. J Cosmet Laser Ther 2015;17:156–61.

30. Varlaro V, Manzo G, Muganini F, Bisacci C, et al. Carboxytherapy: effects on microcirculation and its use in the treatment of severe lymphedema. ACTA Phlebol 2007;8:79–91.

31. Pianez LR, Custódio FS, Guidi RM, de Freitas JN, et al. Effectiveness of carboxytherapy in the treatment of cellulite in healthy women: a pilot study. Clinical. Cosmet Investig Dermatol 2016;9:183–90.

32. Kippenberger S, Loitsch S, Guschel M, Mueller J, et al. Mechanical stretch stimulates protein kinase B/Akt phosphorylation in epidermal cells via angiotensin II type 1 receptor and epidermal growth factor receptor. J Biol Chem 2005;280:3060–7.

33. Wong T, McGrath JA, Navsaria H. The role of fibroblasts in tissue engineering and regeneration. Br J Dermatol 2007;156:1149–55.

Address correspondence and reprint requests to: Noha H. Moftah, MD, Dermatology, STDs and Andrology, Faculty of Medicine, Minia University, Al-Minya, Egypt, or e-mail: nohamoftah2013@yahoo.com