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Review Article

Soft tissue augmentation in atrophic post-acne scars treatment

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Abstract

Acne scars have negative profound impact on the quality of life of patients. Treatment of acne scars should be customized based upon characteristics of the scar, skin type, patient's preferences, and physician's experience. In this article, we comprehensively review the existing evidence for employing soft tissue augmentation in acne scars treatment. We searched PubMed, Medline, Scopus, Embase, Google scholar and Science Direct for articles that evaluated the efficacy of soft tissue augmentation via injection method for the treatment of atrophic acne scars from January 2000 until June 2021. Thirty articles were selected for final evaluation. The materials that were used for soft tissue augmentation in treatment of acne scars included hyaluronic acid-based fillers, autologous fat, polymethylmethacrylate microspheres plus bovine collagen, calcium hydroxylapatite, plasma gel, poly-L-lactic acid, collagen and silicone. Adjuvant treatments included microneedling, high-frequency ultrasound, microfocused ultrasound with visualization, radiofrequency, fractional carbon dioxide laser, erbium-doped yttrium aluminum garnet, fractional Er: glass, subcision and platelet rich plasma. Currently, soft tissue augmentation has gained popularity in treatment of acne scars. Soft tissue augmentation is a minimally invasive procedure that can provide both immediate and gradual improvement and is effective in the treatment of rolling and boxcar scars, while its efficacy is limited in icepick scars. Ideal filler in treatment of atrophic acne scars should have long-lasting effects with minimal side effects or serious complications such as nodule formation and immune system activation.

Key words
Soft tissue augmentation; Post acne scarring; Hyaluronic acid; Autologous fat; Plasma gel.

Introduction

Acne is a common inflammatory skin disease of pilosebaceous unit that affects nearly 85% of adolescents and young adults. Delayed or inadequate treatment especially in severe nodulocystic lesions can lead to scar formation that usually happens in approximately 95% of these patients. Acne scars are classified as post-acne erythema (PAE), post inflammatory hyperpigmentation (PIH), atrophic scars and hypertrophic ones.[1-7] Roughly, more than three-quarter of acne scars are atrophic and the remaining is hypertrophic. It has been postulated that releasing enzymes such as matrix metalloproteinase-2 (MMP-2) via fibroblasts and keratinocytes following a prolonged inflammatory process, results in the destruction of collagen fibers and subcutaneous fat along with periadnexal fibrosis.[4-33]

Depending upon depth, width and topographic features, acne scars are categorized as icepick, rolling or boxcar scars. Icepick scars usually are V-shaped with narrow (<2 mm) and deep configuration, involving deep dermis and subcutaneous area. Rolling scars are generally round-to-oval, shallow, and wide (nearly 4-6

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mm). Boxcar scars are usually wide U-shape scars (1-4 mm) with squared-up borders that, depending on depth, are categorized as shallow (0.5 mm) or deep (>0.5 mm).[4-33] To date, different treatment modalities including resurfacing techniques, subcision, surgical corrections, and fillers have been utilized for the treatment of atrophic acne scars.[4-33] In this article, we comprehensively review the existing evidence for employing soft tissue augmentation in acne scars treatment.

Methods

We searched PubMed, Medline, Scopus, Embase, Google Scholar and Science Direct with the keywords including "acne" AND "scar" AND "injection" AND "filler" OR "soft tissue augmentation" OR "hyaluronic acid" OR" collagen" OR "silicone" OR "polymethylmethacrylate" OR "poly-L-lactic acid" OR "calcium hydroxylapatite" OR "autologous fat" OR "plasma gel". The inclusion criteria were defined as articles that evaluated the efficacy of soft tissue augmentation via injection method in the treatment of atrophic acne scars between January 2000 and June 2021. Basic science articles, review articles, letters to the editor, articles that did not report efficacy or the precise description of the treatment protocol, applied topical fillers, had less than five cases, or *in vitro* and animal studies were excluded from the review. At the first round, seventy-eight articles were found. Two authors evaluated the full text of articles for eligibility. After removing duplicate articles and basic science ones, twenty-five articles were chosen. Five articles were found via searching bibliography of studies. Ultimately, thirty articles were selected for final evaluation. **Figure 1** illustrates search strategy.

Results

Thirty articles including eleven randomized controlled trials (RCT), four comparative studies (three prospective and one retrospective), six non-comparative studies (four prospective and two retrospective), and nine case series (six prospective and three retrospective) were chosen for final assessment. Materials that were used in these studies for soft tissue augmentation included hyaluronic acid-based (HA) fillers (ten articles), autologous fat (five articles), polymethylmethacrylate microspheres (PMMA) plus bovine collagen (four articles), calcium hydroxylapatite (CaHA, four articles), plasma gel (three articles), poly-L-lactic acid (PLLA, two articles), collagen (one article) and silicone (one article). Adjuvant treatments included microneedling, high-frequency ultrasound (HIFU), micro-focused ultrasound with visualization (MFU-V), radiofrequency, fractional carbon dioxide (FCO_2) laser, erbium-doped yttrium aluminum garnet (Er: YAG) laser, fractional Er: glass laser, subcision, and platelet rich plasma (PRP) injection. The results of literature reviews are summarized in **Table 1**.

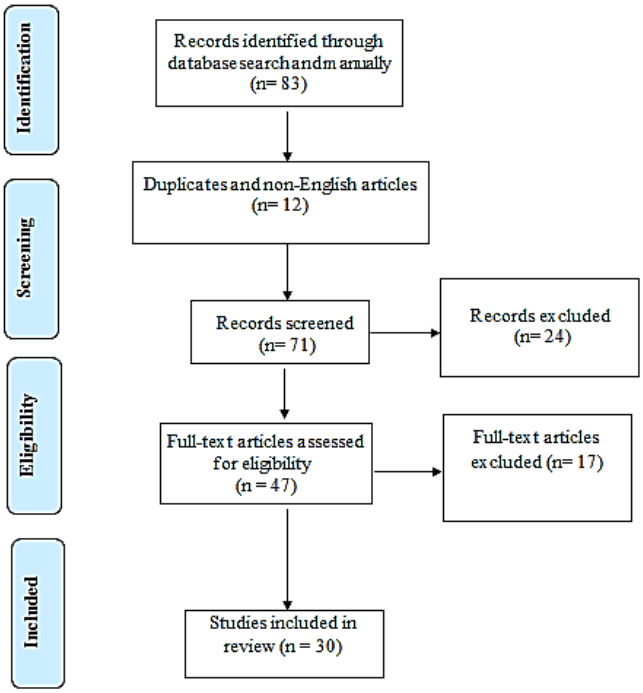

Figure 1 Schematic of the search strategy.

Discussion

Acne scars have negative profound impact on the quality of life of patients. Psychological problems such as social isolation, suicidal ideation, low self-esteem, embarrassment, frustration, depression, and anxiety are observed frequently in patients with acne scar that can disrupt their daily life activities. Despite the presence of different treatment modalities for acne scars, the treatment course is usually time-consuming, expensive, and might lead to complications such as long-lasting edema, swelling, erythema and PIH, especially in the patients with dark skin complexion.[1-33]

Currently, soft tissue augmentation using injection of fillers has gained popularity in treatment of acne scars. This technique has the advantage of both immediate and gradual improvement, the mechanism of which starts by the release of underlying tethered fibrotic tissue as well as immediate filling effects of the filler. The latter can also prevent re-adhesion of fibrotic bands. In addition, these filling products result in neo-collagenesis and epithelialization by stimulating proliferation and migration of fibroblasts and keratinocytes, respectively.[4-33] On the other hand, stretching the skin after injection of dermal fillers provokes differentiation of fibroblasts to myofibroblasts and inhibits apoptosis of these cells which further enhances the augmentation effects. Furthermore, improvements in the overall skin appearance (texture, tone, lightness and laxity) as well as biophysical measurements (i.e. transepidermal water loss, skin hydration, elasticity and flexibility) have been observed along with the treatment course. The rolling and boxcar scars have shown optimal response, while no or only minimal effect was seen in icepick scars.[4-33]

HA-based fillers were the most commonly used fillers for acne scar treatment.[4-13] Histologically, scar treatment using HA fillers has shown to cause an increase in density and thickness of collagen (types of I, III, IV and VII) and elastic fibers along with a reduction in inter-fibrillary dermal space.[4-13,34] Various fillers including Restylane vital, Belotero Basic, Juvederm voluma, Stylage, Esthelis Basic, Viscoderm, and Profhilo were used in acne scars treatment in the reviewed articles.[4-13] One to four treatment sessions were used with 2 to 6-week intervals. The total amount of HA used in each session was between 0.5 cc to2 cc (0.02-0.7 cc/each scar). Auto injectors, needles [27-31 gauges (G)] or cannulas (25-29 G) were used for injection. The level of injection was intradermal or subcutaneous (SQ). Different techniques of injection including fanning, cross-hatch and vertical modified tower (VMT) technique were employed. Injections were performed superficially in facial vascular danger zones such as glabella, forehead, nose and temple.[4-13] Good-to-excellent improvement in acne scars with high level of satisfaction was reported in patients treated with HA-based fillers either as a monotherapy or in combination with lasers (Er: glass, FCO_2 and Er: YAG). Effects of the treatment were remained for 9-14 months after the treatment.[4,7-13] No significant difference was observed between cross-linked HA with non-cross-linked HA in terms of the efficacy of treatment and its durability.[12] HA fillers as an adjuvant to subcision showed better improvement in acne scars in comparison to subcision with or without saline injection.[5,6]

Moreover, the combination of subcision and HA demonstrated equal efficacy compared to combination of subcision and thread.[6] Conversely, in a study, combining FCO_2 laser with non-cross-linked HA was significantly less effective in improving acne scar severity compared with the combination of FCO_2 laser and PRP. However, the patients were satisfied with both treatment methods.[4]

Table 1 The overview of studies evaluating soft tissue augmentation for acne scar revision

Name	*Design*	*Number (sex)*	*Age*	*FST*	*Case group*	*Characteristics of filler/preparation*	*Characteristics of application*	*Control group*	*Type of scar*	*Acne severity*	*Sessions*	*Interval*	*Evaluation methods*	*Results*	*S/E (%)*	*F/UP*
HA																
Mahamoud (2020)[4]	Prospective RCT Split-face Single-blind Evaluator-blind	14 M 16 F	25-44 (30.1 ± 5.49)	3-5	Non-cross-linked HA+ FCO_2	Viscoderm Concentration: 16 mg/cc	Needle: 27 G Level: intradermal	FCO_2+ PRP	NS	Mild-to-severe	3	4 w	Goodman and Baron's grading systems Scar counting Histopathology Patient satisfaction VAS	Higher significant improvement in PRP group compared to HA group	Moderate pain Erythema Down time Edema	3 mo
Mohammed (2022)[5]	Prospective RCT Parallel-group Evaluator-blind	13 M 29 F	19-33 (24.4 ± 2.3)	2-5	Non-cross-linked HA+ subcision	Profhilo 3.2%, 32 mg of HMW-HA + 32 mg of LMW-HA	Needle: 29 G (0.02-0.1 cc/point) Cannula: 25 G (0.02-0.1 cc/point) Level: intradermal Total volume: 0.5-2 cc	Subcision+ saline	Rolling Box car Ice pick	Mild-to-severe	1	NA	Goodman and Baroon's grading scale Patients satisfaction Quartile weighted acne scar severity index scale	Significantly better result with combination therapy compared to monotherapy	Erythema Ecchymosis Edema Bruising	6 mo
Ebrahim (2022)[6]	Prospective RCT Split-face	17 (NS)	21-48 (26.65 ±6.77)	NS	Cross-linked HA+ subcision (3 monthly)	Stylage Concentration: 26 mg/cc	Level: mid-to-superficial dermis Tower technique Total volume: 1.5-2 cc/each side	1) Thread (PLLA)+ subcision 2) Subcision	Box car Rolling	Mild-to-severe	1	NA	Goodman & Baron's qualitative global acne scarring Quartile grading scale Patients satisfaction VAS	Significantly better results in combination groups compared to monotherapy group	Erythema (64.7) Pain (70.6) Edema (70.6) Ecchymosis (64.7)	6 mo
Dierickx (2018)[7]	Prospective Non-comparative	8 F 4 M	27-43 (33)	NS	Cross-linked HA	Restylane Vital+ 0.3% Lidocaine Concentration: 20 mg/cc	Needle: 30 G Multiple retrograde linear /fanning/ cross-hatch techniques Level: intradermal 0.02 cc/point Mean total volume/ session: 3.8 (2-4) cc	No	NS	Moderate-to-severe	3	4 w	SCAR-S GAIS Subject satisfaction	67%: improvement in SCAR-S at F/Up 59%: improvement in GAIS 83%: patients satisfaction	Bruising (16.7) Erythema (41.7) Inflammation (8.3) Hematoma (8.3) Mass (8.3) Nodule (41.7) Pain (16.7) Swelling (25)	9 mo
Halachmi (2013)[8]	Prospective Case series	7 M 5 F	19-54	NS	Cross-linked HA+ ablative laser (FCO_2/Er:YAG)	Restylane Vital Concentration: 20 mg/ml	Micro dermal drupelets Metered dose injector 0.01 cc/point level: superficial dermis	No	Ice pick	Moderate-to-severe	1	NA	Photograph	Immediate improvement	Erythema Edema Pain Pinpoint bleeding	No
Lee (2010)[9]	Prospective Case series Evaluator-blind	6 M 4 F	21-40 (29.2)	2-5	Cross-linked HA	NS	Subdermal minimal surgery (airgent) 20-50/points/session 0.15 cc/shot	No	Rolling Ice pick Boxcar	NS	3	4 w	Quartile grading scale Patients satisfaction	Physician evaluation (Excellent: 20%, good: 60%, moderate: 20%) Patient evaluation (mild: 20%, moderate: 50%, strong: 30%)	Spot bleeding Edema Mild pain (40)	3 mo
Artzi (2020)[10]	Prospective Case series Evaluator-blind	12 (NS)	23-52 (33.2 ± 9)	2-4	Non-cross-linked HA	Profhilo	Needle: 29 G Level: intradermal + Cannula: 25G Level: SQ Total mean volume : 0.5-2 cc 0.02-0.1 cc/point	No	Rolling Boxcar	Moderate-to-severe	2	4 w	Goodman and Baron grading scale Patients satisfaction VISIA VAS	Marked improvement: 16.7% Moderate improvement: 66.6% Minimal	No	6 mo

Name	*Design*	*Number (sex)*	*Age*	*FST*	*Case group*	*Characteristics of filler/preparation*	*Characteristics of application*	*Control group*	*Type of scar*	*Acne severity*	*Sessions*	*Interval*	*Evaluation methods*	*Results*	*S/E (%)*	*F/UP*
														improvement: 16.7%		
Goodman (2016)[11]	Prospective Case series	5 (NS)	19-40	1-4	Cross-linked HA	Juvederm Voluma Concentration: 20 mg/cc	VMT Volume: 1.1 cc (first session),0.5 cc (second session) Needle: 31 G Level: deep dermis 0.02-0.04 cc/point	No	Rolling Ice pick Boxcar	NS	2	2 w	Scar count Patients assessment Physician assessment VAS Goodman and Baron grading scale	68% reduction in scar count Excellent-to-good improvement based on patients and physician assessments	NS	5 mo
MacGillis (2021)[12]	Retrospective Case series	28 F	48.6	NS	Cross-linked/ Non-cross-linked HA	Esthélis Basic (concentration: 22.5 mg/cc) Non-cross-linked HA (concentration: 10 mg/cc) Final concentration: 2.5 mg/cc	Pneumatic jet injection Volume: 0.05-0.75 cc/point Level: intradermal	No	NS	NS	2.8	4-6 w	Patients satisfaction GAIS	High satisfaction: 55%	Pain Discomfort Swelling (8) Bruising Erythema	3.5 mo
Akerman (2022)[13]	Retrospective Case series Evaluator-blind	11 F 1 M	32 - 57 (44 ± 5.2)	1-3	Non-cross-linked HA+ non-ablative laser (1,540-nm, Er:glass,4 weekly sessions)	Profhilo 32 mg HMW-HA +32 mg LMWHA	Volume: 2 cc	No	NS	Mild-to-moderate	2	2 w	Patients satisfaction Physician evaluation VAS Photograph	Mild-to-moderate improvement High patients satisfaction	Erythema, Edema Mild-to-moderate pain	1-3 mo
Lipotransfer																
Tenna (2017)[14]	Prospective RCT	30 (NS)	18-52	2-4	Nano fat+ PRP+ FCO_2	Volume: 7 cc Donor site: lower abdomen/flank/hip/thigh Harvested cannula: 3mm Centrifuge: 3000 rpm for 3 min	Cannula: 19 G	Nanofat+ PRP	NS	NS	2	6 mo	Patients satisfaction (FACE-Q) 22-MHz ultrasound	No significant difference between two groups	NS	6 mo
Azzam (2013)[15]	Prospective RCT Evaluator-blind	5 F 5 M	18-34	3-4	Fat	Harvesting site: Iliac crest Centrifuge: 3,000 rpm × 7 minutes	NS	FCO_2 (3 monthly)	Rolling Icepick Boxcar	NS	1	NA	Photograph Patients satisfaction	Significantly better results in fat injection group	PIH (10) Erythema (10) Malar fullness (30)	3 mo
Abou Eitta (2019)[16]	Prospective Split-face Comparative Evaluator-blind	9 F 1 M	20-45 (33.20 6.51)	1-4	AT-ASCs	Donor site: Abdomen/tthigh/buttock Centrifuge 1) 10 min for 300 g 2)5 min for 300 g Volume: 50 cc	NS	FCO_2 (3 monthly)	Rolling Ice pick Boxcar	Moderate-to-severe	1	NA	Goodman and Baron grading scale Scar area percentage Biophysical measurements Patients satisfaction	No significant difference between two groups	NS	3 mo
Shetty (2021)[17]	Prospective Comparative Evaluator-blind	12 (NS)	20-43 (33.58 ±7.42)	NS	Fat+ subcision	Harvested cannula: 3 mm Site: abdomen Centrifuge: 704 g × 3 min	Fanning technique Level: SQ	PRP+ subcision (3 monthly)	Ice pick Rolling Box car	Mild-to-severe	1	NA	Goodman & Baron's quantitative global acne scarring grading system Patients satisfaction VAS	No significant difference between two groups	Pain Edema Erythema (100) Bruising (100)	3 mo
Nilforoushzadeh (2022)[18]	Prospective Case series	9 (NS)	NS	NS	Autologous fat+ SVF+ PRP	Donor site: hip/ lower abdomen/thigh Aspirated fat: 100 cc Harvested cannula:2.4 mm	Cannula: 18 G Level: SQ Volume: 50 cc	No	Rolling	NS	1	NA	Biometric assessment (skin ultrasound imaging system, mexameter, cutometer,visioface) Patients satisfaction	66.6% : well satisfied 22.3%: moderate satisfied	NS	6 mo

Name	*Design*	*Number (sex)*	*Age*	*FST*	*Case group*	*Characteristics of filler/preparation*	*Characteristics of application*	*Control group*	*Type of scar*	*Acne severity*	*Sessions*	*Interval*	*Evaluation methods*	*Results*	*S/E (%)*	*F/UP*
PMMA																
Biesman (2019)[19]	Prospective RCT	18 F 5 M	23-64 (40.67 6 13.12)	1-6	PMMA+ Microneedling	Bellafill	Tunneling/retrograde linear threading, serial puncture techniques Needle: 26 G Mean total volume: 2.6± 1.9 cc Mean volume/scar: 0.1± 0.2 (ranging from 0.01 to 0.9) cc	Microneedling (3 weekly sessions)	NS	NS	1-2	4 w	GAIS ASAS Quality of life assessment tool Subject scar impact scale questionnaire 3-D imaging	Significantly better improvement in combination group compared to monotherapy group	No	24 w
Karnik (2014)[20]	Prospective RCT Parallel design Double-blind	57 M 90 F	44	NS	PMMA	Artefill	Level: reticular dermal level/ dermal-SQ Junction Retrograde linear threading /serial puncture technique 0.11 cc/each scar/session Maximum average in 2 sessions: 0.42 cc	Saline	Rolling	Moderate-to-severe	2	4 W	ASRS PGAIS SGAIS Patients satisfaction	Significant improvement in PMMA group compared to saline group	Pain (2.1) Bruising (2.1) Swelling (1.1) Acne (1.1)	6 mo
Joseph (2019)[21]	Prospective Open-label Non-comparative Pilot	26 F 16 M	22-70 (42)	1-6	PMMA	Bellafill	Total volume: 2.72 (0.16–9.2) Mean volume/scar: 0.09 cc (0.01-0.51)	No	NS	NS	1-2	4 w	GAIS ASAS QOLIS	High patients and physician satisfaction	Hypopigmentation (2.38) Hyperpigmentation (2.38) Ecchymoses (2.38) Bruising (2.38)	7 mo
Solomon (2021)[22]	Retrospective Non-comparative	96 (NS)	NS	NS	PMMA± laser/subcision	Bellafill	Mean number: 1.6 cc	No	NS	No	1-3	NS	Patients satisfaction	Patients satisfaction: 99%	Nodule (1/04)	2 y
CaHA																
Antonino (2021)[23]	Prospective RCT Double-blind	10 F	31-46 (39.2 ± 4.19)	NS	CaHA+ HIFU	Radiesse	Level: SQ 0.1 cc/point 30 microdropletes Needle: 30 G Volume: 3 cc	Saline + HIFU	NS	Moderate-to-severe	1	NA	Vectra H2 Antera 3-D Photograph Patients satisfaction	Significant improvement in CaHA group compared to saline group at first mo No significant difference between two groups at F/UP	No	6 mo
Koren (2019)[24]	Retrospective Comparative Evaluator-blind	189 (NS)	25.3 _ 5	2-4	CaHA± EBD	0.8 cc Radiesse+ 0.2 cc lidocaine+ 1 cc sterile saline	VMT (for boxcar and ice pick) linear droplets technique (rolling)	EBD	Rolling Boxcar Ice pick	NS	1	NA	PGAIS SGAIS Patients satisfaction VISIA	Significantly better results along with lower number of treatment sessions with combined FCO_2 + CaHA	Erythema PIH	NS
Casabona (2018)[25]	Retrospective Non-comparative Pilot	10 (NS)	23-55 (37.6 ±10.0)	NS	CaHA + MFU-V	Radiesse Reconstructed with 1.5 cc lidocaine	Volume/ side: 1.5 cc Cannula: 25 G Fanning technique with microdropletes deposition	No	NS	Moderate-to-severe	1	NA	Goodman and Baron grading scale Patient satisfaction	Significant improvement compared to base-line 90%: very satisfied 10%: satisfied	No	3 mo

Name	*Design*	*Number (sex)*	*Age*	*FST*	*Case group*	*Characteristics of filler/preparation*	*Characteristics of application*	*Control group*	*Type of scar*	*Acne severity*	*Sessions*	*Interval*	*Evaluation methods*	*Results*	*S/E (%)*	*F/UP*
Goldberg (2006)[26]	Prospective Case series	10 (NS)	18-60	NS	CaHA	Radiesse	Needle: 27 G Level: mid-deep dermis Total volume: 0.1-0.3 cc	No	Rolling Boxcar Ice pick	NS	1-2 (3/12)	4 w	Photograph	Good-to-excellent improvement in scars that maintain at F/UP No response in ice pick scar	Erythema (8.3) Extrusion of filler (33.3)	12 mo
Plasmagel																
Nassar (2022)[27]	Prospective Comparative Split-face Single-blind	18 F 8 M	19-40 (29.15 ± 5.61)	NS	Plasma gel + subcision	8 cc blood Centrifuge: 3500 g × 10 min hot water: 70° ×3 min 90° × 10 min Cold water: 25° × 30 min	Needle: 18 G Fanning technique	PRP+ subcision	Boxcar Ice pick Rolling	Mild-to-severe	4	4 w	Goodman and baron qualitative grading system Photograph Patients satisfaction GAIS	Significantly better results with plasma gel after first session and at F/UP period based on Goodman score No significant difference between two groups based on GAIS and patient satisfaction	Ecchymosis (34.6) Swelling (100) PIH (15.4) Persistence of hematoma/nodule formation (7.7) Recurrence (11.5)	6 mo
Elfar (2020)[28]	Prospective RCT Single-blind	16 F 4 M	20-37 (26.70 _ 5.03)	NS	Plasma gel	10 cc blood Centrifuge: 1) 15 minutes × 72 g 2)5 minutes × 1006 g 6.5 cc PPP+ 0.5 cc PRP Hot water (60°-100°) × 1 min Cold water: 8°-0° × 1 min	Level: intradermal/SQ Volume: 2-4 cc Insulin syringe	Plasma gel + microneedling Microneedling (dermaroller)	Boxcar Rolling icepick	NS	4	4 w	Histology IHC Goodman's Quantitative score	Significant improvement in plasma gel groups as monotherapy or combined at the end of study compared to base-line Significant improvement in F/UP only with combined treatment	No	3 mo
Mohammed (2022)[29]	Prospective RCT	5 M 5 F	22-35 (26.4 ±4.4)	NS	FCO_2 + plasma gel injection	10 cc blood Centrifuge: 1) 1500 rpm×10 minutes 2) 10 minutes × 3500 rpm Hot water (70°-100°): 3 min Cold water: 5°-0°: 3 min	Needle: 24 G Angle: 45 Level: intradermal Volume: 3 cc	1) FCO_2+ topical plasma gel 2)FCO_2	Boxcar Rolling Icepick	NS	4	4 w	GSGS GAIS patients satisfaction DLQI	Significantly better results based on GCGS in combined of plasma gel group as topical or injection with FCO_2 at the end of study and F/UP No significant difference between three groups based on GAIS , patients satisfaction and DLQI	Pain Edema Erythema Crust	6 mo
PLLA																
Sapra (2015)[30]	Prospective Non-comparative Open-label Evaluator-blind	13 F 9 M	37.6± 9.17	NS	PLLA	Sculptra 10 cc dilution (fanning technique) 5 cc dilution (depot technique) Reconstructed with	Needle: 25 G Fanning technique in SQ level/depot technique in supraperiosteal level Total volume: 37.0 6±	No	NS	NS	3-4	4 w	PSIS BESIS SASIS Patients satisfaction VISIA-CR camera Likert scale	Patients satisfaction: 54.5%: very good-to-excellent (54.5%) PSIS: Excellent-to-very	Nodule (4.5)	6 mo

Name	*Design*	*Number (sex)*	*Age*	*FST*	*Case group*	*Characteristics of filler/preparation*	*Characteristics of application*	*Control group*	*Type of scar*	*Acne severity*	*Sessions*	*Interval*	*Evaluation methods*	*Results*	*S/E (%)*	*F/UP*
						sterile water, lidocaine-epinephrine	5.08 Mean volume/session: 9.5 cc							much improvement (63.6%) BESIS/SASIS: excellent-to-much improvement (68.2% / 44.5%)		
Beer (2007)[31]	Prospective Non-comparative Open-label	10 M 10 F	42.4 7± 10.7	NS	PLLA	Sculptra Reconstituted with 4 cc of sterile water and 1mL of lidocaine with 1:100,000 epinephrine	Level: deep Dermis/ dermal-SQ junction Mean volume: 0.4-0.7 cc (0.1-1.5 cc)	No	Rolling Ice pick	Moderate-to-severe	7	4 w	Beer Global Scarring Index Size of scar Patients satisfaction	Significant reduction based on physician Marked improvement based on patients evaluation	No	No
Collagen																
Sage (2011)[32]	Prospective RCT Split-face Single-blind Evaluator-blind	10 (NS)	33-65 (50)	2-5	Collagen	Dermicol-p35 (Evolence)	Needle: 27 G Volume: 0.5 cc	Subcision	Rolling	Ns	1	NA	Photograph Physician global assessment Patients global assessment VAS	Significant difference only with patients evaluation at 3-month F/UP	Pain (0.5) Erythema (0.8) Swelling (1) Discoloration (0.6) Bruising 0.7) Lumpiness (1.4)	6 mo
Silicone																
Barnett (2005)[33]	Retrospective Case series	3M 2 F	23-42 (30.6)	NS	Liquid silicone	Viscosity : 350-centistokes	Microdroplet, multiple injection technique Level: deep dermis/superficial SQ Needle: 25-27 G inch Total volume: 0.4-1.8 cc 0.02-0.1 cc/point	No	NS	NS	1-6	4 w	Photograph	Significant improvement	Bruising Overcorrection Discoloration	10-30 y

Abbreviations: FST, Fitzpatrick's skin type; S/E, side effect; F/UP, follow up; HA, hyaluronic acid; RCT, randomized controlled trial; M, male; F, female; FCO_2, fractional carbon dioxide laser; G, gauge; PRP, platelet-rich plasma; w, week; mo, month; HMW, high molecular weight; LMW, low molecular weight; NA, not applicable; NS, not stated; VMT, vertical modified technique; PLLA, poly-L-lactic acid; VAS, visual analogous scale; SCAR-S, scale for acne scar severity; GAIS, global aesthetic improvement scale; Er:YAG, erbium-doped yttrium aluminum garnet; SQ, subcutaneous; PIH, post inflammatory hyperpigmentation; AT-ASCs, Autologous adipose tissue-derived adult stem cells; SVF, stromal vascular fraction; PMMA, polymethylmethacrylate; ASAS, acne scar assessment scale; ASRS, acne scar rating scale; QOLIS, subject quality of life scar impact scale; CaHA, calcium hydroxylapatite; HIFU, high-frequency ultrasound; EBD, energy-based device; MFU-V, microfocused ultrasound with visualization; PPP, platelet-poor plasma; IHC, immunohistochemistry; DLQI, dermatology life quality index; GCGS, global scarring grading system ; PSIS, physician's scar improvement scale; BESIS, blinded evaluator's scar improvement scale ; SASIS, self-assessed scar improvement scale ;

Autologous fat injection has the advantages of easy availability, biocompatibility, and good integration of fat into the surrounding tissue. In addition, autologous fat contains pluri-potent stem cells that can differentiate to various types of cells such as fibroblasts, keratinocytes, or endothelial cells via up regulation of transforming growth factor (TGF)-β1, TGF-β3, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and keratinocytes growth factor (KGF).[14-18] The main disadvantages of autologous fat grafting are the unpredictable survival rate of transferred fat cells and its time-consuming harvest procedure.[14-18] Significant improvements in acne scars, biophysical measurements and skin density were demonstrated with the combination of fat transfer, stromal vascular fraction (SVF) and PRP.[18] Additionally, combination of one session of subcision with fat transfer showed equal efficacy compared with combining three sessions of subcision with PRP injection.[17] Moreover, fat transfer demonstrated superior or equal efficacy compared to FCO_2 laser and had lower percentage of complications and needed fewer treatment sessions.[15,16]

Polymethyl methacrylate (Bellafill, Artefill) Collagen-based dermal fillers with polymethyl methacrylate (PMMA), composing PMMA microspheres in 3.5% bovine collagen, is the only Food and Drug Administration (FDA)-approved filler for the treatment of acne scars. The size of microspheres ranges fromapproximately 30 to 50 µm in order to escape from phagocytosis, and therefore, preventing stimulation of immune system. Prior to injections, however, skin test is recommended due to the presence of bovine collagen in the filler composition.[19-22] Significant improvement was demonstrated in acne scars treated with injection of PMMA as either monotherapy or in combination with laser, subcision or microneedling as compared with base-line measures or the control group (saline injection or microneedling). The improvement was assessed using subjective tools, starting at two weeks after the second injection and continuing during 6 months follow up.[19-22] Patients with darker skin phototype had a better response rate than the other skin types that can be due to the thicker dermis in dark skin patients.[21] Treatment sessions varied from 1 to 3 sessions with four weeks intervals. The injection volume varied from 0.16-9.2cc (0.01-0.9 cc/scar). Injections were performed with 26 G cannula and via tunneling technique (retrograde linear injection) or serial puncture being done at the level of deep dermis or the junction of dermis and SQ area.[19-22]

Calcium hydroxylapatite (Radiesse) Calcium hydroxylapatite (CaHA) constitutes an aqueous gel carrier and CaHA particles (with about 25-45 µmin diameter). Immediate effect appears by aqueous gel, while stimulation of neocollagenesis results in more persistent filling effects.[23-26] Optimal results in acne scar treatment were reported with a combination of one session HIFU and CaHA injection, compared with combined HIFU and saline injection at one-month follow up. However, the difference between the two groups was not statistically significant at 6months follow up.[23] Significantly higher improvements were observed in acne scars after fewer number of treatment sessions with combination of CaHA and energy-based devices (EBD) including FCO_2, non-ablative fractional laser (1540 nm), and radiofrequency, as compared with monotherapy with EBD. The best results were achieved when the filler was injected before EBD, especially with 2 to 4weeks intervals as compared with the concomitant use of both EBD and filler. As for FCO_2 laser, a 6-week interval between sessions of laser therapy was

accompanied with optimum results.[24] Injections were performed via 25-27 G cannula or 30 G needle at deep dermis/ SQ level during monthly sessions. Total injected volume ranged from 0.1 to 3 cc (0.1cc/scar) in each session. Fanning, VMT, towering, micro-droplet and linear techniques were used for injection. VMT and linear retrograde techniques were preferred over the other methods of injection for treatment of boxcar/ icepick scars and rolling scars, respectively.[23-26]

Plasma gel contains growth factors and cytokines that provoke angiogenesis, activation of fibroblasts, keratinocytes and neocollagenesis. These factors include transforming growth factor (TGF)-β1, TGF-β3, and epidermal growth factor receptor (EGFR). Additionally, healing and soothing effects has been demonstrated via up regulation of hepatic growth factor (HGF) and TGF-β, and through down regulation of AP-1 and C-FOS.[27-29] Plasma gel has also vasoconstrictive effects that can reduce erythema after resurfacing procedures, and can also reduce edema via attachment of angiopoietin-1 to tie-2 receptor. Plasma gel can constitute from either PRP or platelet poor plasma (PPP). Compared with PRP, PPP has lower levels of growth factors and cytokines, while containing higher ratio of fibrinogen and fibrin. It results in slow release of growth factors from attached platelets to fibrin network and provides a better efficacy compared with PRP.[27-29] Intradermal injection of plasma gel leads to significant improvement in acne scars. However, the result was not maintained after three months follow-up.[27-29] Adding either plasma gel injection or topical plasma gel to FCO_2 laser was accompanied with a significantly higher improvement in acne scars compared with FCO_2 laser alone.[29] In addition, a combination of subcision and plasma gel showed a significantly better outcome compared with subcision and PRP that was assessed using Goodman and Baroon's grading system.[27]

Poly (L-lactide) (Sculptra) Poly (L-lactide) (PLLA) is a lyophilized powdered vicryl substance that requires reconstitution with distilled water before application. Proper injection technique, high dilution, and vigorous massage are recommended when using PLLA in order to reduce the risk of nodule formation. In the reviewed studies, PLLA was diluted with 5-10cc sterile water. The 5-cc dilution was used for supraperiosteal injection, and the 10-cc dilution was used for SQ application.[30,31] The diluted substance was usually kept at the room temperature from two hours to two days before injection to prevent the risk of nodule formation.[30,31] Published articles demonstrated good-to-excellent improvement using physician's evaluation in nearly half of the patients. Additionally, significant reduction in the size and severity of acne scars was demonstrated at the end of the treatment course that was maintained for 24 months afterwards.[30,31] The best results were observed in rolling scars with a 2-3 mm depth at most. Histologically, an infiltration of inflammatory cells (lymphocytes, macrophages, and fibroblasts) in the periphery of a vascularized capsule (encompassing microparticles) has been demonstrated in PLLA application that ultimately stimulates collagenesis and scar improvement.[30,31] The treatment sessions varied between 3 to 7 at monthly intervals. The total volume of 0.1 to 9.5 cc/session was applied via 25 G needles using fanning (for subcutaneous injection) or depot (for supraperiosteal injection) techniques.[30,31]

Collagen (Evolence) Evolence is a naturally purified porcine cross-linked collagen that is manufactured via Glymatrix technology. Thereby, in contrast to the other kinds of collagens, it does not require any preceding skin tests and provides a longer duration of action

(roughly one year). In Sage *et al.* study, injections were performed via needles (size of 27 G) with a total volume of about 0.5 cc per each session.[32] They compared the efficacy of collagen injection with that of subcision. They showed a significantly higher efficacy in the treatment with subcision at 3-month follow up using patients' global assessment. In contrast, there was no significant difference between the two groups based on physician's global assessment at the same follow up session. Bruising was reported significantly higher in subcision group, while lumpiness was observed more frequently in collagen group.[32]

Liquid silicone Silicone is composed of units of dimethyl silicone and trimethylsilicone. As a benefits, silicone can be applied precisely based on the size and shape of the skin defect and provides a long-lasting effects. In a case series, liquid silicone (350 centistokes) was used for acne scars (1- 6 times with monthly intervals) and it resulted in significant improvement in acne scars. The results were persistentfor10-30 years follow up period. Multiple microdroplets injection method was used for placement of the filler at the deep dermis/ SQ level. Injections were delivered via needle (25-27 G) with a total volume of 0.4-1.8 cc (0.02-0.1 cc/scar).[33]

Safety considerations Several side effects of scar treatment have been reported following soft tissue augmentation method including pain, erythema, edema, swelling, pinpoint bleeding and bruising. These sign and symptoms, however, were temporary and resolved during nearly one week without any treatment. Nodule formation and lumpiness were reported in application of plasma gel (when combined with subcision), cross-linked HA, PLLA and PMMA in 3.6%, 2.8%, 2.4% and 0.3% of cases, respectively. Other side effects included hypopigmentation (PMMA), hyperpigmentation (PMMA), acne formation (PMMA), overcorrection (silicone), malar fullness (fat transfer) and extrusion of filler material (CaHA).[4-33]

Conclusion

Selecting the optimum treatment approach for atrophic acne scars is challenging. Treatment should be tailored to the type of scar, patients' skin phototype, preference of patients (treatment cost and recovery time) and physician's experience. Soft tissue augmentation is a minimally invasive procedure that has short downtime with both immediate and relatively long-term effects. It is a suitable treatment method for rolling and boxcar scars, while its efficacy is limited for icepick scars. Ideal fillers for treatment of atrophic acne scars should have long-lasting effects with minimum side effects and lowest rate of serious complications such as nodule formation, granulomas, allergic reaction, and migration of the implanted filler.

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