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Amniotic fluid-derived mesenchymal stem cell products combined with microneedling for acne scars: A split-face clinical, histological, and histometric study

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Abstract

Background: Postacne scars are still a challenge in its management. Microneedling is a popular minimally invasive technique in treatment of such scars. However, the addition of topical stem cell products after microneedling is considered a new treatment regimen for these scars.

Objective: To compare efficacy of amniotic fluid-derived mesenchymal stem cell-conditioned media (AF-MSC-CM) and microneedling vs microneedling alone in management of atrophic acne scars.

Methods: Ten cases with atrophic postacne scars received five sessions of microneedling, with 2-week interval on both sides of the face. Then, AF-MSC-CM was topically applied to right side of the face after microneedling. Clinical examination with histopathological and computerized histometric analysis was done 1 month after the sessions.

Results: There was significant increase in the improvement percentage of acne scars on right side (dermaroller and AF-MSC-CM) vs left side of face (dermaroller; $P < 0.001$). Histologically, improvement of character of collagen and elastic fibers was noticed, especially on right side. Meanwhile, significant increase in epidermal thickness on both sides of face was detected.

Conclusion: Amniotic fluid-derived mesenchymal stem cell-conditioned media combined with microneedling is more effective in management of atrophic postacne scars than microneedling alone.

KEYWORDS
acne scars, amniotic fluid stem cells products, dermaroller, growth factors, microneedling

1 | INTRODUCTION

Stem cells are undifferentiated cells with self-renewal and differentiation as a repair system of the body. These cells are classified into adult, embryonic, and fetal types.[1] Fetal stem cells have major advantages as they are multipotent with high expansion and low immunogenic properties, and they do not require an addition of growth factors for their culture.[2] Amniotic fluid, being derived easily from the developing fetus during scheduled amniocentesis at the second trimester of gestation, contains multiple fetal mesenchymal stem

cells, which may be considered an important source of stem cell therapy.[3]

Cell-based therapies using stem cells and their products of growth factors are considered a therapeutic strategy to repair the abnormal damaged tissue through their proposed direct cellular effect in addition to complex paracrine mechanisms by secretion of different extracellular matrix molecules, interleukins, growth factors, and other proteins.[4] Specifically, amniotic fluid-derived mesenchymal stem cells (AF-MSC) produce various cytokines and chemokines, which are known to be important in normal wound healing in cosmetic dermatology, including interleukin (IL)-8, IL-6, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF).[3]

The function of these growth factors in skin aging is well-documented[5]; however, its role in atrophic acne scars is considered an emerging novel treatment modality since few human studies discussed their clinical efficacy without any objective evaluation.

Acne scars represent a major complaint of many people as it occurs in about 30%[6]-95% of acne patients,[7] and it affects the psychology and life of any individual.[8] These acne scars may be hypertrophic or atrophic types, depending upon whether they are elevated or depressed in relation to skin surface.[9] Atrophic postacne scars are further divided into three basic variants, including icepick, rolling, and boxcar.[10]

Treatment of atrophic postacne scars is a problem that faces each physician. Accordingly, different therapeutic procedures are widely designed to stimulate neocollagenesis and scar remodeling, including chemical peeling, dermabrasion, microdermabrasion, microneedling, punch grafting, scar excision, and lasers.[8]

Almost all growth factors are large hydrophilic molecules more than 20 kDa; so, they penetrate the epidermis in very low quantities. Accordingly, its cutaneous application should be accompanied with transdermal delivery systems,[11] as dermaroller (DR)[5] that creates pinhole wounds using many microneedles through the epidermis into the papillary dermis. These wounds cause release of many growth factors and initiate the normal process of wound healing, leading to new collagen production and skin tightening. Moreover, DR causes damage of the old collagen strands connecting the scars to the upper dermis, leading to improvement of scars.[12]

This study aims to compare clinically and histologically the efficacy of AF-MSC-conditioned media (CM) after microneedling vs skin microneedling alone in management of atrophic acne scars.

2 | MATERIALS AND METHODS

2.1 | Patients

This prospective split-face study included 10 cases, with facial atrophic postacne scars. They were recruited from the Dermatology clinic of Minia University Hospital. Informed consents were obtained from all patients. The Ethical Committee and the Committee for Postgraduate Studies and Research of Faculty of Medicine at Minia University approved this study.

Complete clinical examination was done. Patients with some dermatological diseases as active acne, eczema, psoriasis, verrucae, recurrent herpes virus infection, or keloidal tendency and with blood diseases were excluded from this study. Meanwhile, cases taking anticoagulant therapy, topical drugs (within previous 1 month), oral isotretinoin, or using laser or light-based therapy (within previous 6 months) were also excluded.

2.2 | Treatment protocol

Firstly, anesthesia was done by application of lidocaine/prilocaine 2.5% cream (EMLA cream; AstraZeneca AB) to the whole face and occlusion 1 hour before skin microneedling. Then, EMLA was gently removed with sterile wet gauze and the face was painted with 1% povidone iodine (Betadine) solution and cleansed with sterile saline.

Five sessions of microneedling with DR were done on both sides of face, at 2-week interval. The DR used had 192 needles arranged in eight rows, with 1.5-mm needle length, 0.25-mm needle diameter at the penetration point and 20 mm width and diameter of the roller head (Model MF8, MDD 93/42 EEU). Rolling was performed for 10 times in each direction (vertical, horizontal, and both diagonal directions), with stretching the skin in a perpendicular direction to skin microneedling movement to reach the base of postacne scars. Appearance of erythema and pinpoint bleeding was considered the end points of the session.

At the end of microneedling of the right side of the face, AF-MSC-CM (1 mL, BIO STEM CM Cell Signal Therapy Scar Control kit, Bio Innovation Holdings Limited, STEM Medicine) was gently applied and left to dry for 15 minutes.

Then, application of Fusidic acid ointment was done for 24 hours (Fucidin ointment; LEO Pharma) to prevent secondary bacterial infection. After that, an emollient cream was used until disappearance of erythema. The use of sunscreens with sun protection factor (SPF) ≥50 was essential during the course of treatment and 1 month after the end of sessions.

2.3 | Clinical evaluation

Clinical response was assessed after 3 months of starting treatment (1 month after the end of sessions) by two blinded dermatologists. The clinical improvement in atrophic acne scars appearance was estimated and evaluated based on a five-point score (none = 0%, mild = 1%-25%, moderate = 26%-50%, good = 51%-75%, and very good = 76%-100%).[2] Moreover, count of the total and different types of acne scars was performed, before and after treatment on both sides of the face, and the percent of reduction was calculated.[13]

Adverse effects, including erythema, edema, crusting, pigmentary changes, ecchymosis, and scarring, were examined at each visit.

2.4 | Histopathological examination

Skin biopsy specimens were taken; using 3-mm punch probes, from both sides of face prior to treatment and 1 month after the end of

sessions from the nearest point to pretreated biopsy. Then, each biopsy was fixed in formalin 10%, embedded in paraffin, and sectioned into 5-µm-thick sections. These sections were stained with hematoxylin and eosin (H&E), Masson trichrome (for collagen fibers), and Orcein (for elastic fibers) stains. Examination and photographing of the sections were done using a light microscope (Accu-Scope # 3025 five headed [A3025-5]-Olympus) with a built-in camera (Olympus; digital camera E-330 SLR).

2.5 | Morphometric measurement of epidermal thickness

The epidermal thickness was calculated using a computer-based software histometry (analysis®Five by Olympus Soft imaging solutions GmbH). The mean value was calculated by determination of five measurements for each section between top of granular cell layer to dermo-epidermal junction.[14]

2.6 | Statistical evaluation

For statistical analysis of the data, SPSS for Windows was used (Version 16.0.1; SPSS Inc). Range and mean ± standard deviation (SD) were calculated for quantitative data, whereas number and percent were expressed for qualitative data. Paired *t* test, independent student *t* test and chi-square test, Spearman's rho correlation, Mann-Whitney test, Kruskal-Wallis test, and Wilcoxon signed-rank test were done for the data. Significance was expressed in terms of *P*-value, which was significant when it was ≤0.05 and highly significant when ≤0.001.

3 | RESULTS

This study included 10 patients, with facial atrophic acne scars (5 [50%] males and 5 [50%] females). Their age ranged from 25 to 36 years (30.5 ± 3.69). Regarding Fitzpatrick skin typing, three had skin type III (30%) and seven patients (70%) had skin type IV.

3.1 | Clinical assessment

At 1 month after the end of sessions, there was highly significant increase in improvement percentage of right side (65.40 ± 11.34) vs left side of face (38.60 ± 9.02; $P < 0.001$; Figure 1; Table 1).

By grading the improvement percentage, significant difference was also noticed on left side of face (DR) as they had moderate improvement in 80% and good improvement in 20% of patients ($P = 0.008$). Meanwhile, significant difference was also noticed on the right side of the face (DR and AF-MSC-CM) as they showed moderate improvement in 20%, good improvement in 60%, and very good improvement in 20% of patients ($P = 0.003$). Most patients demonstrated improvement in skin texture on both sides of the face, with better improvement on right side ($P = 0.007$; Figure 1; Table 1).

By counting the acne scars, a significant decrease in the count of total scars was noticed on both sides of the face at 1 month after the end of sessions compared with baseline ($P = 0.005$). Regarding types of acne scars, there was significant decrease in all types of acne scars on right (boxcar $P = 0.005$; icepick $P = 0.007$; and rolling $P = 0.004$) and left sides of the face (boxcar $P = 0.006$; icepick $P = 0.008$; and rolling $P = 0.005$). Regarding the percent of reduction, it was significantly increased in boxcar and rolling types compared with ice pick on

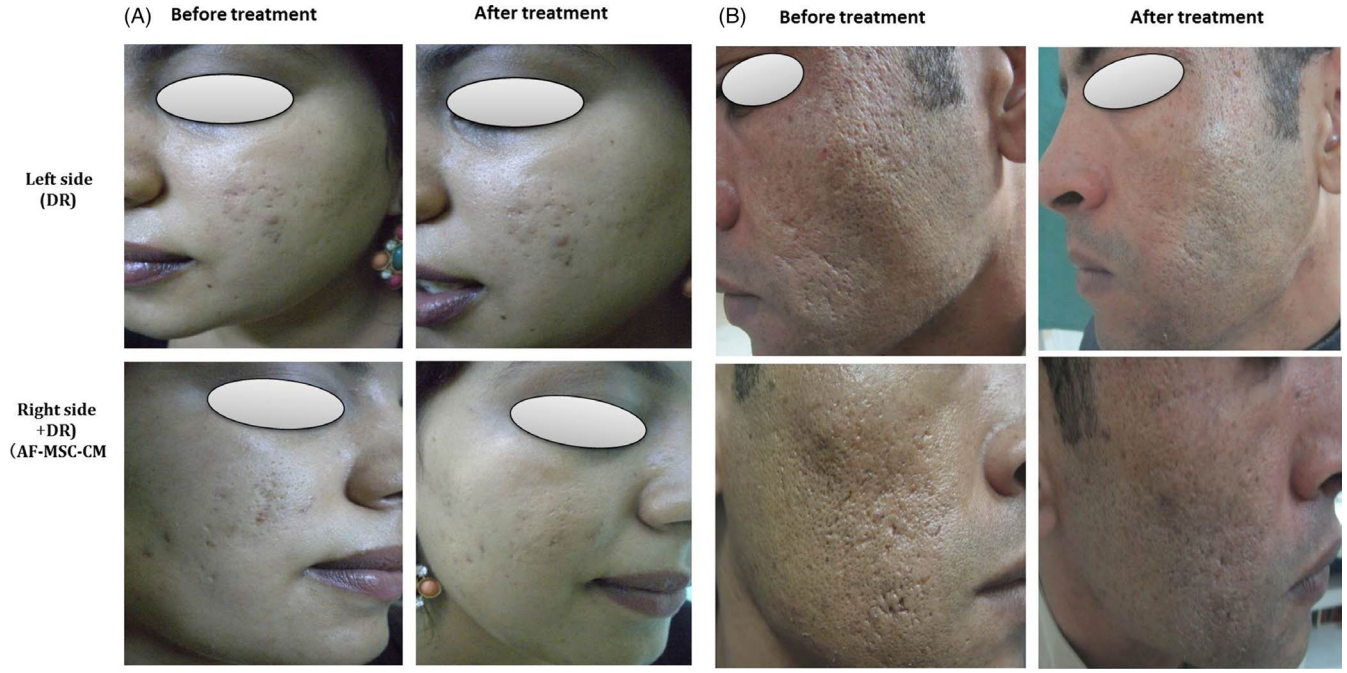

FIGURE 1 Female (A) and male (B) cases with postacne scars before and after treatment. Left side of face (DR only) show moderate (A) and good improvement (B). Meanwhile, right side of face (AF-MSC-CM and DR) has very good improvement (A, B). AF-MSC-CM, amniotic fluid-derived mesenchymal stem cell-conditioned media; DR, dermaroller

TABLE 1 Clinical improvement in atrophic postacne scars on both sides of face

Acne scars	Left side (DR)	Right side (DR + AF-MSC-CM)	*P* value
Improvement per cent			
Range	30-53	50-85	<0.001**
Mean ± SD	38.60 ± 9.02	65.40 ± 11.34	
Score (%)			
Very good	0 (0)	2 (20)	0.007*
Good	2 (20)	6 (60)	
Moderate	8 (80)	2 (20)	
Mild	0 (0)	0 (0)	
P value	0.008*	0.003*	

Abbreviations: AF-MSC-CM, amniotic fluid-derived mesenchymal stem cell-conditioned media; DR, dermaroller.
*Significant value.
**Highly significant value.

both sides (right $P = 0.001$ and left $P = 0.005$). Meanwhile, the right side showed significant increase in the reduction percentage compared with the left side of total and each individual type of scars (boxcar $P = 0.043$; icepick $P = 0.002$; rolling $P = 0.010$, and total $P = 0.001$).

There were no significant correlation between the clinical response and both the patients' age and their skin type of the right side ($r = 0.218$, $P = 0.545$ and $r = 0.218$, $P = 0.545$, respectively) and left side of the face ($r = 0.442$, $P = 0.201$ and $r = 0.345$, $P = 0.329$, respectively). Meanwhile, a significant correlation was obtained between the clinical response and the duration of acne scars on the right ($r = 0.701$, $P = 0.024$) and left sides of the face ($r = 0.886$, $P = 0.001$).

3.2 | Adverse effects

Erythema and slight edema have been encountered on both sides of the face after each session, and they disappeared completely after 1-2 days. Meanwhile, lymph node enlargement (pre- and postauricular) was noticed in only one patient (10%) on the right side (DR and AF-MSC-CM) after 2 days of the 5th session and resolved within few weeks after receiving a broad-spectrum antibiotic for 6 days. At 1 month after sessions, there were no adverse effects on both sides of the face.

3.3 | Histopathological results

3.3.1 | Collagen fibers (Masson trichrome stain)

Before treatment, collagen bundles were disorganized on both sides of the face, with increased interfibrillary spaces. One month after sessions, both sides of face showed increase in deposition of collagen bundles, which became more fine and organized with decreased interfibrillary spaces. Improved characters of collagen bundles were better noticed on right side (combined treatment) vs left side of the face (DR; Figure 2).

3.3.2 | Elastic fibers (Orcein stain)

In pretreated biopsy, the dermis showed increase in abnormal elastic fibers, which were in contact with epidermis on both sides of face. After treatment, the content of abnormal elastic tissues decreased, with the appearance of the newly synthesized elastic fibers, which appeared fine and well organized, especially on right side of face (Figure 3).

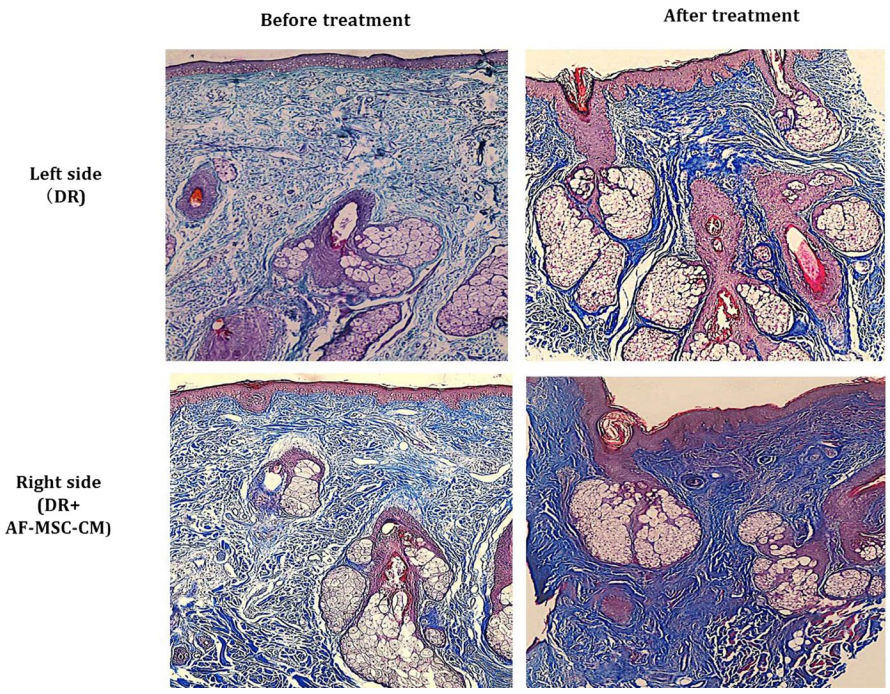

FIGURE 2 Collagen fibers.Pretreated biopsies showing disorganized collagen bundles with increased interfibrillary spaces on both sides. After treatment, post-treated biopsies demonstrate more dense collagen fibers, which become finer and assembled in a normal lattice distribution with darker stain and decreased interfibrillary spaces, especially on right side of face (AF-MSC-CM and DR; Masson trichrome, ×200). AF-MSC-CM, amniotic fluid-derived mesenchymal stem cell-conditioned media; DR, dermaroller

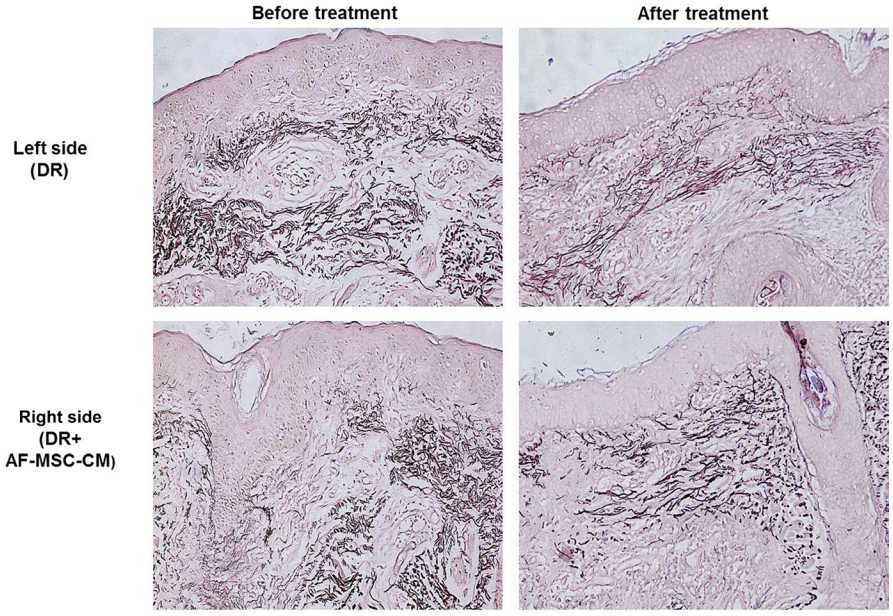

FIGURE 3 Elastic fibers. Pretreated biopsies showing dense abnormal elastic tissue near the epidermis on both sides of face. After treatment, post-treated biopsies demonstrate less abnormal elastic material, which are moved downwards in the dermis with appearance of the newly synthesized elastic tissue, which become finer and well organized, especially on right side of face (combined treatment; Orcein, ×100). AF-MSC-CM, amniotic fluid-derived mesenchymal stem cell-conditioned media; DR, dermaroller

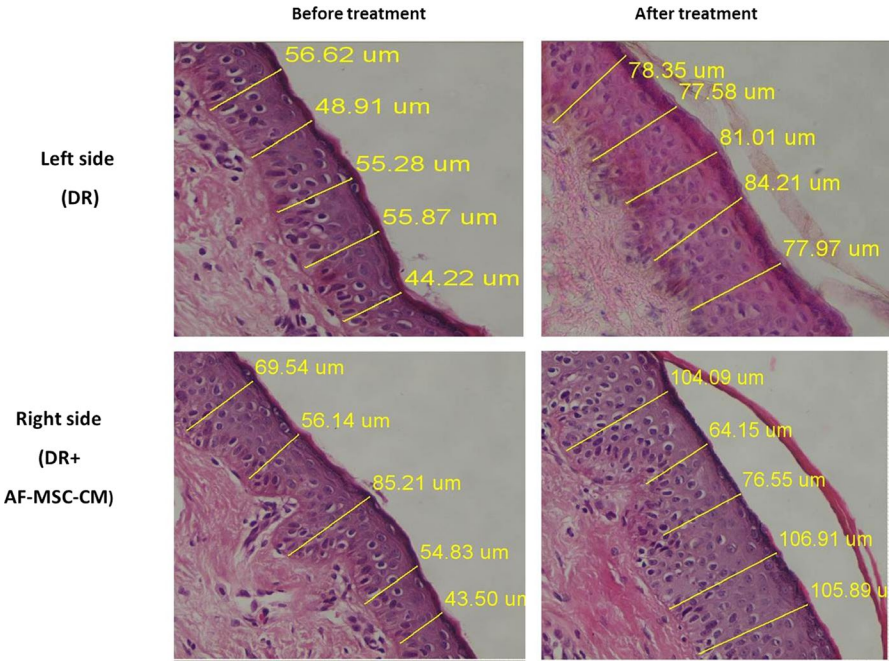

FIGURE 4 Histometry of acne scars biopsies showing increase in epidermal thickness on both sides of the face after treatment when compared to pretreated biopsies. However, there was no significant difference between both sides of the face (H&E, ×400). AF-MSC-CM, amniotic fluid-derived mesenchymal stem cell-conditioned media; DR, dermaroller

3.4 | Histometric results

A highly significant increase in the mean epidermal thickness was detected and ranged from 61.36 ± 4.9 μm before treatment to 72.98 ± 6.51 μm at 1 month after treatment on the left side of the face (DR; $P = 0.001$). Also, a highly significant increase in the mean epidermal thickness was demonstrated from 62.23 ± 4.16 μm before treatment to 75.67 ± 6.56 μm after treatment on right side (combined group; $P < 0.001$), with no significant difference to left side of face ($P = 0.37$; Figure 4; Table 2).

4 | DISCUSSION

Management of acne scars represents a challenging dermatological condition, and it often needs a multimodal approach to achieve desirable results.[15] Accordingly, new combination methods, which denote the use of two or more different techniques, will be preferred for more potentially optimizing outcomes with minimal adverse effects.[16]

Microneedle technology (transdermal delivery) overcomes the stratum corneum barrier and is considered a minimally invasive and painless modality of cosmetic therapy. Moreover, microneedling was

TABLE 2 Histometric results of mean epidermal thickness (μm) before and after sessions on both sides of the face in patients with acne scars

Epidermal thickness (μm)	Left side (DR)	Right side (DR + AF-MSC-CM)	*P* value
Before treatment			
Range	52.18-69.59	56.10-69.22	0.68
Mean ± SD	61.36 ± 4.9	62.23 ± 4.162	
After treatment			
Range	61.2-82.1	65.1-85.10	0.37
Mean ± SD	72.98 ± 6.51	75.67 ± 6.56	
P value	0.001**	<0.001**	

Abbreviations: AF-MSC-CM, amniotic fluid-derived mesenchymal stem cell-conditioned media; DR, dermaroller.
**Highly significant value.

reported to improve atrophic acne scarring in a nonablative method, avoiding all side effects and prolonged down time of all invasive techniques.[17]

Cell therapies and tissue engineering show great promise in wound repair and scar management. Meanwhile, the cutaneous application of these growth factors requires transdermal delivery system like DR[5] because they are large and hydrophilic molecules.[12] So, the present study aimed to compare clinically and histopathologically the efficacy of topically applied AF-MSC-CM after skin microneedling for management of atrophic acne scars.

At 1 month after last session, a highly significant increase in the improvement percentage of atrophic acne scars was detected on right side of the face (65.40%), which was treated by both DR and AF-MSC-CM, when compared to left side (38.60%), treated only by DR By staging this improvement percentage, the combined treatment method gave score of improvement of very good (20%), good (60%), and moderate (20%). On the other hand, DR treatment showed less satisfactory results with score of improvement ranging from good (20%) to moderate (80%). Meanwhile, almost all patients showed improvement in skin texture at both sides of the face, with better improvement on the right side.

Indeed after DR only, this study is similar to many studies showing that the degree of the acne scars was significantly reduced in most treated cases.[1,2,5,12,16] On reviewing the literature, no previous reports evaluating AF-MSC-CM with microneedling were present for management of atrophic acne scars. However, Cotsarelis et al[18] evaluated the effect of autologous adult bone marrow stem cells, which were injected intradermally into atrophic acne scars, and they showed significant improvement. Another study, using adipose-derived stem cell conditioned media (ADSC-CM) combined with fractional ablative CO_2 laser for atrophic postacne scars, showed increase in patient satisfaction, skin hydration, and elasticity associated with scar improvement.[19]

After each session of microneedling in the present study, transient erythema and edema were detected on both sides of the face, and they disappeared 1-2 days later, as described in previous studies.[20-22] Meanwhile, the right side of one case showed pre-auricular and postauricular lymph node enlargement after the 5th session of combined treatment (DR and AF-MSC-CM), and they resolved within few weeks after receiving a broad-spectrum antibiotic. This lymphadenopathy may be explained by infection or immunologic reaction to the conditioned media that should be further evaluated in future larger studies.

At 1 month after last session, no photosensitivity and postinflammatory hyperpigmentation were detected since the epidermis remains intact following microneedling.[13,14]

Histologically, quantitative histometry on both sides of face revealed significant increase in epidermal thickness after treatment, with no significant difference between them. This agrees with many subjective microneedling studies,[1,8,20,21] as well as El-Domyati et al,[16] who objectively reported an increase in the epidermal thickness after microneedling in acne scars. This means that microneedling performs significant effect on the epidermis, whereas AF-MSC-CM exerted no or minimal additional effect on epidermal thickness.

The dermis is formed mainly of collagen (80%-85% of dermis) with a little amount of elastic fibers (1%-2% of dermis) forming regular network. The collagen has an important function in skin strength and elasticity,[23] while the elastic tissues are essential for stretching and recoiling of the skin.[24]

In this study, at 1 month after treatment, an increase in the distribution of collagen bundles was observed, and they became finer and assembled in normal lattice distribution with decreased interfibrillary spaces, especially on the right side of face. Meanwhile, there was marked decrease in abnormal elastic material, and fine newly synthesized elastic fibers appeared, especially on right side of face. These results agree with various studies evaluating the histological effects of microneedling on atrophic postacne scars.[14]

On reviewing literature, there were the absence of previous reports evaluating the efficacy of AF-MSC-CM on collagen and elastic fibers in biopsies taken from acne scars patients. However, Zhou et al[19] observed increase in dermal collagen and normal elastin density and arrangement, but after the use of ADSC-CM and fractional ablative CO_2 resurfacing for atrophic acne scars. This confirms that combination of AF-MSC-CM and DR act mainly through dermal remodeling as well as fractional CO_2 and ADSC-CM.

The significant better clinical and histological dermal improvement observed on right side (combined) vs left side of the face (DR) may be attributed to the additive or synergistic role of AF-MSC-CM beside DR This media contains different cytokines and chemokines, including IL-6 and 8, TGF-β, TNF-α, VEGF, and EGF, that are critical in wound healing and cell proliferation especially of fibroblasts and collagen synthesis.[3] In addition, MSCs secrete angiogenic and antifibrotic factors and factors responsible for extracellular matrix homeostasis such as matrix metalloproteinases.[25]

The authors are aware that one of the limitations of this study is the relatively small number of patients; however, the results showed evidence of better clinical and histological improvement with combined treatment. Further trials with larger cohort of patients and a longer follow-up period are mandatory to confirm such findings.

In conclusion, combined use of AF-MSC-CM with microneedling proved to be more effective both clinically and histologically in management of atrophic postacne scars than microneedling alone. This may be explained by that AF-MSC-CM could augment the efficacy of microneedling by decreasing abnormal elastic fibers and increasing collagen synthesis (collagen induction therapy), mainly through the effect of growth factors.

CONFLICT OF INTEREST

No conflict of interest.

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