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Micro-Needling Plus Human Placental Extract and Mesenchymal Stem Cell Mesotherapy Versus Micro-Needling in the Treatment of Atrophic Post Acne Scars

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Abstract

Atrophic acne scarring is a prevalent cosmetic issue that may affect 95% of acne patients. It is to assess the effectiveness of human placental extract (HPE) and mesenchymal stem cells (MSC) mesotherapy combined with microneedling versus microneedling alone for the treatment of atrophic acne scars. Thirty patients with post-acne scars participated in the trial. On both sides of the face, microneedling was done. The left half of the face received microneedling and human placental extract (HPE) and mesenchymal stem cells (MSC), while the right half of the face received microneedling. There were a total of 4 treatment sessions administered over 3 weeks. The final analysis of the data was conducted using the quantitative and qualitative scales developed by Goodman. The study involved 30 participants, After treatment, the severity of the acne scars on both sides was statistically significantly reduced according to Goodman and Baron's qualitative and quantitative methods. Right and left halves showed 38.54 ± 18.29 and 56.13 ± 15.25 improvements respectively, on Goodman's Quantitative scale. On the right half of the face, Goodman's Qualitative Scale revealed excellent response in 3 of patients, good response in 16, and poor response in 11 patients, while on the left half of the face, excellent response was seen in 14 of patients, good response in 10, and poor response in 6 of patients. We concluded that mesotherapy with human placental extract (HPE) and mesenchymal stem cells (MSC) is effective in the treatment of atrophic acne scars.

Keywords: Mesotherapy; Microneedling, Post acne scars.

1. Introduction

Acne is a common skin disease that affects both adolescents and adults. It is a multifactorial disease with comedones, papules, pustules, nodules, and scars as symptoms [1]. Acne scarring can occur as a result of inflammatory damage to the connective tissue of acne-affected skin. Scaring from acne has a significant negative impact on the quality of life of young adults [2]. It may be associated with severe psychological distress [3]. Acne scars are divided into two types: hypertrophic and atrophic. Atrophic acne scars are classified as icepick, rolling, or boxcar [4].

Acne scar treatment options include surgical techniques (punch grafting, punch excision, and subcision), resurfacing techniques (dermabrasion, ablative laser treatment, and chemical peels), non-ablative laser treatment, radiofrequency, autologous fat transfer, and dermal filler injection [5]. The human placenta is a vast reservoir of bioactive molecules. Some common human placental extracts contain keratinocyte growth factor or endothelial cell growth stimulators. The presence of bioactive peptides such as endothelin-1 (ET-1) adrenocorticotropic hormone (ACTH), and sphingolipids, which are well-known modulators of various cellular responses, has already been documented in the human placenta.Endothelin-1(ET-1) is a versatile peptide that was discovered as a vasoactive component but has since been shown to have significant mitogenic, dendricity-inducing, and melanogenic13 activities on melanocytes [6]. Mesenchymal stem cells (MSCs) appear to be immune privileged and have therapeutic potential in cell therapy [7]. Mesenchymal stem cells (MSCs) have a trophic effect on cell regeneration and tissue repair, which has been scientifically proven to reduce hypertrophic and atrophic acne scars. [8]. Because of the lack of ethical concerns, the high availability, and the growing number of methods for isolating and expanding such cell types, Mesenchymal stem cells (MSCs) appear to be an ideal source for tissue engineering applications. [9]

2. Patients and Methods

The study was carried out on 30 patients suffering from atrophic post acne scars on their faces.

2.1 Study type

The study type was split face single blinded, comparative study.

2.2 Study place

The patients were picked from Dermatology and Venereology outpatient clinic in Al-Zahraa University hospital.

2.3 Study period

The study was conducted from March to November 2021.

2.4 Inclusion criteria

- Age: 18–40 years old.
- Patients of both sexes.
- No concurrent topical or systemic treatment for post acne scars during the last 3 months preceding the study.
- Patients with mild to severe atrophic post acne scars.
- Patients with Fitzpatrick skin type up to IV.

2.5 Exclusion criteria

- Pregnancy and lactation.
- Patients with active inflammatory acne lesions.
- Patients using drugs causing photosensitivity or systemic retinoid in the previous 6 months.
- Evidence or history of keloid scars.
- Photosensitive dermatoses are like solar keratosis.
- Chronic diseases (coagulation defects, blood disease, diabetes and collagen diseases).
- Active infection in the treatment area such as wart or herpes simplex.
- Premalignant or malignant lesions in the treatment area.
- Unrealistic expectations.

2.6 Sampling Method

A random sampling

2.7 Sample size

30 patients

2.8 Study procedures

Before beginning the study, the research ethical committee of Al-Azhar University's faculty of medicine for girls approved it. Data was recalled in a confidential manner

and the privacy of all patients was maintained.

Each patient provided written informed consent after being informed about the steps of the procedure, the expected effects, potential complications, other alternative treatments, and the importance of photo documentation.

Complete history was taken including personal history (age, sex, residence and special habits), present history about medical and dermatological diseases, age of onset of acne, duration of post acne scarring, family history of acne and post acne scarring and medications taken over the past 6 months.

Local examination was performed with a magnifying lens under good lighting to detect the location, size, and type of acne scars, while the patient sat upright to detect the type of each lesion. Photos were taken at the start of treatment, before each session, and two months later, using the same camera settings and lighting as before (Oppo Reno 3).

The physician clinical assessment, patient evaluation, and image analysis were used to evaluate post-acne scars before the start of treatment, before each treatment session, and two months after the last treatment session. Grading of atrophic acne scars was done according to Goodman and Baron qualitative and quantitative acne scarring grading system before and after treatment [10, 11]. The Qualitative scale is divided into four severity levels based on the type of lesion, visibility of the lesion, and depth of the scar (1-4). The Quantitative scale is a further modification of the above that is based on the individual lesion count and scores them from 0 to 84 [12].

2.9 Treatment Protocol

Prior to the procedures, a thick layer of topical anaesthetic cream (Pridocaine cream-a mixture of lidocaine 2.5 percent and prilocaine 2.5 percent) was applied to the treated area under occlusion for 30 minutes. The entire face was then cleansed with a gentle cleanser.

Lesions on both sides of the face were treated with micro needling with a dermapen device (A6) at a depth of 1.5 ml. The derma pen device was applied to the skin with one hand while stretching the skin with the other to reach the base of the scars. Rolling was done seven times in each direction (vertical, horizontal, and both diagonal directions) and four times in each direction (horizontally, vertically, and diagonally right and left, stamping) until uniform pinpoint bleeding was seen. After each session, the device was cleaned with alcohol. Derma pen was performed every 3 weeks for 4sessions. It was passed in various directions with minimal pressure. After completing Microneedling, left side of the face was applied with 1 ml human placental extract and mesenchymal stem cells mesotherapy **(**Medical Cure Company) and was gently applied and left to dry for 15 minutes.

2.10 Post procedure care

Patients were instructed to avoid soaps and topical creams on the first day. Topical antibiotic cream (Fucidin cream) was applied one day after the procedure for three days. Using 50+ sunscreens between and after sessions was recommended for photo protection.

3. Evaluation

Every session and 2 months after the last session, the clinical response to treatment was evaluated by a physician′s clinical assessment using Goodman and Baron qualitative and quantitative acne scaring grading systems, evaluation of feedback and side effects by patients, photographic evaluation, and by a blind investigator using patients′ photographs before and after treatment.

3.1 Evaluation of the response

After the treatment regimen was completed, the scar photos were assessed and graded by a blinded dermatologist two months later and compared to the pre-treatment period.

Any changes in scar grading were noted using the Goodman and Baron qualitative acne scarring grading system.

If the change was noted as a two-grade reduction, the improvement would be considered excellent. If there was a one-grade reduction in the grade of acne scarring, the improvement was considered good; otherwise, the improvement was considered poor, as proposed (Table 1).

Table 1: Assessment of improvement according to Goodman and Baron qualitative acne scarring grading system

Improvement	Reduction
Excellent	Two grades
Good	One grade
Poor	No reduction

If the scale was reduced by 0-5 points, the reduction was considered minimal; if the reduction was 5-10 points, it was considered moderate; if the reduction was 10-15 points, it was considered good; and if the reduction was more than 15 points, it was considered very good (Table 2) [13].

Table 2: Assessment of improvement according to Goodman and Baron quantitative acne scarring grading system

Improvement state	Reduction
Minimal reduction	0-5
Moderate reduction	6-10
Good reduction	11-15
Very good reduction	More than 15

Table 3: Assessment of improvement by patient satisfaction Patient satisfaction scale:

- **Grade 0** Slight improvement < 25%
- **Grade 1** Moderate improvement 25%-49%
- **Grade 2** Significant improvement 50%-74%
- **Grade 3** Marked improvement ≥ 75%

3.2 Side effects

All patients provided subjective evaluations of the side effects for each side of the face, as they were asked verbally and evaluated by the physician about side effects such as downtime, persistent erythema, oedema, post-inflammatory hyperpigmentation, pain, and others such as scarring, milia, and infections. They were asked to rate the side effects at each session and at the first and second follow-up visits, and pain was scored using a 0-10 pain intensity numeric rating scale (NRS) at the end of each session.

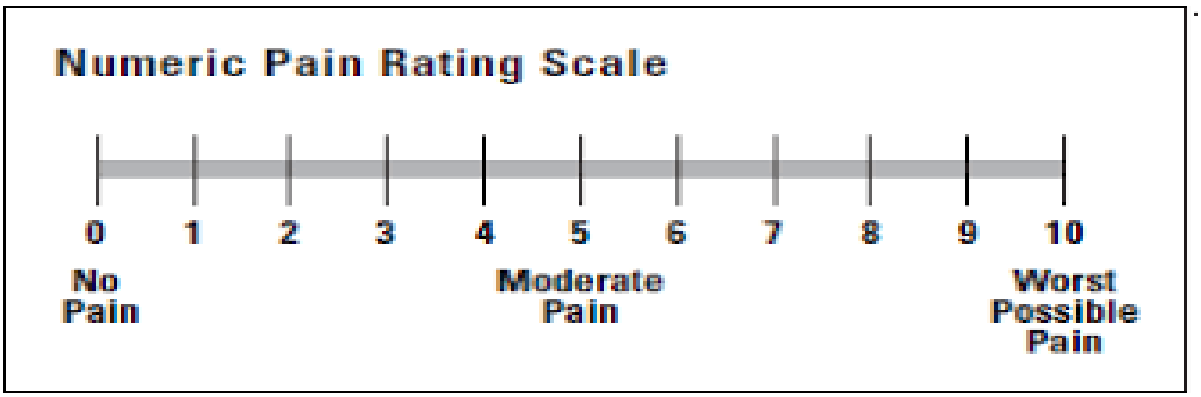

Figure 1: Pain intensity numeric rating scale (NRS).

Figure 2: Female patient aged 25 years old with atrophic acne scars A, B treated by microneedling and C, D treated by microneedling + human placental extract and mesenchymal stem cells mesotherapy (rolling type predominate), skin type 3:

A. Before treatment, Grade 4
B. After 2 months of treatment Grade 2 with excellent improvement
C. Before treatment, Grade 4
D. After 2 months of treatment, Grade 2 with excellent improvement

Figure 3: Female patient 22 years old with atrophic acne scars A,B treated by microneedling and C,D treated by microneedling + human placental extract and mesenchymal stem cells mesotherapy (Box type predominate), skin type 3:

A. Before treatment, Grade 4
B. After 2 months of treatment Grade 2 with excellent improvement
C. Before treatment, Grade 4
D. After 2 months of treatment, Grade 1 with Excellent improvement

4. Results

As show in table 4 from the patients, 20 were females (66.7%) and 10 were males (33.3%), their ages ranged from 19 to 34 years (Mean ± SD: 26.23 ± 7.17). 22 patients (73,3%) was skin type 3 and 8 patients (26.7%) was skin type 4 .7 patients (23.3%) had positive family history of post acne scars and 23 patients (76,7%) had negative family history of post acne scars. As shown in table 5 a total of 5 patients (17%) had Box scars. 6 patients (20%) had ice pick scars .4 patients (13%) had rolling

scars and 15 patients (50%) had mixed types of scars. scar duration ranged from 3-17 years. There were 25 patients (83%) who had skin scar colour, 3 patients (10%) had erythematous scar colour and 2 patients (7%) had pigmented scar colour. As shown in table 7 there was highly statically significant improvement of acne scars grades after treatment with microneedling when compared with them before treatment regarding Goodman qualitative acne scaring grading system (P value <0.01),it was noticed that the sever degree of acne scars showed reduction after treatment with microneedling (from 66.7% to 20.0%), the macular, moderate and the mild degree showed elevation (from 0 to 3.3%), (26.7 % to 50.0%) and (from 6.7% to 26.7%) respectively.

As show in table 8 the next table shows that there was highly statically significant improvement of acne scars grades after treatment with microneedling + mesotherapy when compared with them before treatment regarding Goodman qualitative acne scaring grading system (P value <0.01),it was noticed that the sever degree of acne scars showed marked reduction after treatment with microneedling + mesotherapy (from 66.7% to 16.7%), the macular and the mild degree showed elevation (from 0 to 23.3% and from 0% to 36.7%) respectively and the moderate degree showed moderate improvement (from 33.3 % to 23.3%). As shown in table 9 there was statistically significant difference between both studied groups concerning acne scar grades after treatment regarding Goodman qualitative improvement (P value <0.05), it was noticed that scar improvement was better after treatment with microneedling + mesotherapy more than microneedling only. As shown in table 10 there was high statistically significant improvement of acne scars after treatment with microneedle ng when compared with them before treatment regarding Goodman qualitative scaring grading system (P-value < 0.01). As shown in table 11 there was high statistically significant improvement of acne scars after treatment with microneedling + mesotherapy when compared with them before treatment regarding Goodman qualitative acne scaring grading system (P-value < 0.01). As show in table 12 there was statistical significant better patients satisfaction in microneedling + mesotherapy side more than microneedling side it was noticed that in the left side 13 patients (43%) estimated their response as marked improvement, 9 patients (30%) as significant, 5 patients (17%) as moderate and 3 patients (10%) as slight improvement, in the right side 3 patient (10%) estimated their response as marked improvement, 12 patients (40%) as significant, 9 (30%) as moderate and 6 patients (20%) as slight improvement. patient's satisfaction correlates also with the improvement in skin texture and homogeneity. As shown in table 13 there was statistically significant difference found between microneedling only and microneedling with topical Human placental extract mesotherapy regarding quantitative grading after treatment with p-value =0.039 and there is highly statistically significant difference found between both groups regarding improvement of quantitative grading with p-value <0.001. The table also shows that the quantitative grading in microneedling only and microneedling with topical Human placental extract mesotherapy was highly significantly improved after treatment with p-value <0.001 and <0.001 respectively.

Table 4: Demographic data and history of the patients studied.

No. = 30		
Age	Mean±SD	26.23 ± 7.17
	Median (IQR)	24 (19 – 34)
	Range	19 – 38
Sex	Female	20 (66.7%)
	Male	10 (33.3%)
Type of skin	III	22 (73.3%)
	IV	8 (26.7%)
Family history	No	23 (76.7%)
	Yes	7 (23.3%)

Table 5: Scar parameters among the studied patients

No. = 30		
Scar type	Box scar	5 (16.7%)
	Ice pick scar	6 (20.0%)
	Rolling scar	4 (13.3%)
	Mixed	15 (50.0%)
Scar duration	Median (IQR)	4.5 (3 – 12)
	Range	3 – 17
Scar color	Skin color	25 (83.3%)
	Erythematous	3 (10.0%)
	Pigmented	2 (6.7%)

Table 6: Pain score, percentage of complications and history among the studied patients after treatment

No. = 30		
Pain score	Median (IQR)	5 (3 - 7)
	Range	1 – 9
Complication	No	21 (70.0%)
	Yes	9 (30.0%)
Active acne		3 (10.0%)
Erythema which resolved		4 (13.3%)
Oedema which resolved		2 (6.7%)
Intake of isotretenoine	No	24 (80.0%)
	Yes	6 (20.0%)
Previous treatment	No	20 (66.7%)
	Yes	10 (33.3%)

Table 7: Comparison of acne scar grades before and after treatment with Microneedling only

Micronmicroneedling		Scar grade before		Scar grade After treatment		Test value*	P-value	Sig.
		No.	%	No.	%			
Qualitative grading	Macular	0	0.0%	1	3.3%	14.269	0.003	HS
	Mild	2	6.7%	8	26.7%			
	Moderate	8	26.7%	15	50.0%			
	Sever	20	66.7%	6	20.0%			

Table 8: Comparison of acne scar grades before and after treatment with Microneedling + Mesotherapy

Microneedling + mesotherapy		Scar grade Before		Scar grade After		Test value*	P-value	Sig.
		No.	%	No.	%			
Qualitative grading	Macular	0	0.0%	7	23.3%	27.529	0.000	HS
	Mild	0	0.0%	11	36.7%			
	Moderate	10	33.3%	7	23.3%			
	Sever	20	66.7%	5	16.7%			

Table 9: Comparison between Microneedling group and Microneedling + mesotherapy group regarding acne scar improvement

Qualitative grade Improvement	Right side (Micro needling)		Left side (Micro needling + Mesotherapy)		Test value*	P-value	Sig.
	No.	%	No.	%			
Poor	11	36.7%	6	20.0%	9.973	0.007	S
Good	16	53.3%	10	33.3%			
Excellent	3	10.0%	14	46.7%			

Table 10: Comparison between acne scar improvement before and after treatment with Microneedling side

Qualitative grading		Improvement of Qualitative in microneedling side						Test value	P-value	Sig.
		Poor		Good		Excellent				
		No.	%	No.	%	No.	%			
Before	I	0	0.0%	0	0.0%	0	0.0%	3.932	0.415	NS
	II	2	18.2%	0	0.0%	0	0.0%			
	III	3	27.3%	4	25.0%	1	33.3%			
	IV	6	54.5%	12	75.0%	2	66.7%			
After	I	0	0.0%	0	0.0%	1	33.3%	26.114	<0.001	HS
	II	2	18.2%	4	25.0%	2	66.7%			
	III	3	27.3%	12	75.0%	0	0.0%			
	IV	6	54.5%	0	0.0%	0	0.0%			
Chi-square test	X^2	0.000		20.000		6.000				
	P-value	1.000		0.000		0.111				

Table 11: Comparison between acne scar improvement before and after treatment with Microneedling + mesotherapy

Qualitative grading		Improvement of Qualitative in microneedling +msotherapy						Test value	P-value	Sig.
		Poor		Good		Excellent				
		No.	%	No.	%	No.	%			
Before	I	0	0.0%	0	0.0%	0	0.0%	0.986	0.611	NS
	II	0	0.0%	0	0.0%	0	0.0%			
	III	1	16.7%	4	40.0%	5	35.7%			
	IV	5	83.3%	6	60.0%	9	64.3%			
After	I	0	0.0%	0	0.0%	7	50.0%	40.052	<0.001	HS
	II	0	0.0%	4	40.0%	7	50.0%			
	III	1	16.7%	6	60.0%	0	0.0%			
	IV	5	83.3%	0	0.0%	0	0.0%			
Chi-square test	X^2	0.000		10.400		28.000				
	P-valu	1.000		0.000		0.000				

Table 12: Comparison between microneedling only and microneedling with topical Human placental extract mesotherapy regarding patient's satisfaction.

Satisfaction	(Micro needling)	(Micro needling + Mesotherapy)	Test value	P-value	Sig.
	No. = 30	No. = 30			
Median (IQR)	1.5 (1 – 2)	2 (1 – 3)	-2.632‡	0.008	HS
Range	0 – 3	0 – 3			
Grade 0	6 (20.0%)	3 (10.0%)	8.821*	0.032	S
Grade 1	9 (30.0%)	5 (16.7%)			
Grade 2	12 (40.0%)	9 (30.0%)			
Grade 3	3 (10.0%)	13 (43.3%)			

Table 13: Comparison between microneedling only and microneedling with topical Human placental extract mesotherapy regarding quantitative grading before and after treatment and its improvement

Quantitative		Right side (Micro needling)	Left side (Micro needling + Mesotherapy)	Test value	P-value	Sig.
		No. = 30	No. = 30			
Before	Mean ± SD	18.63 ± 7.24	20.33 ± 5.54	-1.022•	0.311	NS
	Range	9 – 50	11 – 37			
After	Mean ± SD	11.27 ± 5.15	8.87 ± 3.49	2.112	0.039	S
	Range	4 – 28	4 – 22			
% of reduction	Mean ± SD	38.54 ± 18.29	56.13 ± 15.25	4.043	<0.001	HS
	Range	9.52 – 73.68	18.52 – 80			
Reduction	Minimal	11 (36.7%)	4 (13.33%)	8.896*	0.031	S
	Moderate	13 (43.3%)	10 (33.33%)			
	Good	5 (16.7%)	10 (33.33%)			
	Very good	1 (3.3%)	6 (20.0%)			
Paired t-test		8.748	12.420			
P-value		<0.001 (HS)	<0.001 (HS)			

4. Discussion

There were no studies using human placental extract mesotherapy in atrophic acne scars in the literature, but there is a case report by Phonchai et al (2020) [14], A 35-year-old female with atrophic acne scars on both cheeks received subcutaneous injections of human placental extract and mesenchymal stem cell mesotherapy. After subcision on both sides of the face, 0.1 - 0.3 ml was intradermally injected under each scar, and the results of 6 months follow up showed that the texture, pore, and skin complexity were improved by at least 80%, and the qualitative scarring grading score improved, which agreed with our study.

However, El-Domyati et al., (2019) [15] compared the effect of amniotic fluid derived mesenchymal stem cell in the right side with microneedling by derma roller and derma roller only in the left side and they showed significant improvement in the right side with estimated improvement (65.40%) and (38.60%) in the left side. These results were higher than our result might be due to they did 5 sessions but in our study we did 4 sessions only.

Another study, Cotsarelis et al. (1990) [16], looked at the effect of autologous adult bone marrow stem cells injected intradermally into atrophic acne scars and found that they improved significantly. Another study, Zhou et al., (2016) [17], found that adipose-derived stem cell conditioned media (ADSC-CM) combined with fractional ablative CO2 laser for atrophic post acne scars improved patient satisfaction, skin hydration, and elasticity. In the microneedling side 19 patients(63%) showed good improvement and poor in 11 patient (36%) it was noticed that the severe degree of acne scars showed reduction after treatment with microneedling (from 66.7% to 20.0%), the macular, moderate and the mild degree showed elevation (from 0 to 3.3%), (26.7 % to 50.0%) and (from 6.7% to 26.7%) respectively. A significant increase in the improvement percentage of atrophic acne scars was detected by quantitative Goodman and Baron (38.54 ± 18.29). There was a comparable study reported by Asif et al., (2016) [15] in which 50 patients with atrophic acne scars who were treated with split face manner, microneedling was performed on both halves of the face. PRP was applied on right side of the face, while distilled water was applied on the left side of the face. Three sessions were given at an interval of one month. Three months after the final session the side treated with distilled water and microneedling showed excellent response in 10% of the patients, good response in 84% of the patients and no improvement in 6% of the patients and the mean of Goodman quantitative scores of the group treated by microneedling was 45.84% improvement after treatment. Our result was higher than this result may be because we made 4sessions, but this study made 3 sessions only.

Our findings were consistent with those of Ali et al., (2019) [18], who investigated the efficacy of microneedling alone versus chemical peel combined with skin needling in a comparative randomised trial; 60 patients were randomly assigned to one of three groups: Twenty patients were treated with dermapen (group I), twenty patients with Jessner's solution peeling (group II), and twenty patients with dermapen and Jessner's solution (group III) and reported good improvement before and after treatment in the microneedling group.

Another study was conducted by Amer et al., (2021) [19] who compared in forty one patients platelet rich plasma (PRP) with microneedling in the right side and non-cross linked hyaluronic acid in the left side in four sessions at one month intervals and reported that all patients tolerated the procedure well, yet a few adverse effects were noted; four patients showed acne flare-up, four patients showed erythema, four patients complained from pain and two from burning sensation. This study was higher than our study especially on the right side as we used microneedling only but agreed with our study in left side favor that human placental extract effective as non-cross linked hyaluronic acid. And also

agreed with our study that there was no PIH and combination therapy has more result than microneedling only.

We found that patient's satisfaction score correlated greatly with the result as after the fourth session, in the left side 13 patients (43%) estimated their response as marked improvement, 9 patients (30%) as significant, 5 patients (17%) as moderate and 3 patients (10%) as slight improvement, in the right side 3 patient (10%) estimated their response as marked improvement, 12 patients (40%) as significant, 9 (30%) as moderate and 6 patients (20%) as slight improvement. patient's satisfaction correlates also with the improvement in skin texture and homogeneity. Regarding the types of scars, we found that the rolling type was improved than ice pick and box car scars may be due to microneedling technique in our study.

Our findings corresponded with those of Dogra et al., (2014) [20] who discovered improvement in all grades of severity and types of atrophic acne scars, with rolling scars showing the greatest improvement. This could be because he used microneedling techniques in his research.

Fabbrocini et al., (2009) [21], did a study and discovered that skin needling improves acne rolling scars immediately. The severity grade of rolling scars was greatly reduced in all patients, and there was an overall improvement in aesthetics.

Regarding side effects, all patients tolerated the surgery well; nevertheless, three patients experienced acne flare-ups, four experienced erythema, two experienced oedema, and no one experienced post-inflammatory hyperpigmentation (PIH).

El-Domiaty et al. (2015) [22] also stated that all patients had facial oedema and mild pain after the microneedling, which was resolved 24 hours later on the second day, and that there was only minimal erythema, which resolved entirely in 1-2 days. Patients were able to resume normal daily activities two days after the microneedling surgery, which is consistent with our findings.

5. Conclusion

Microneedling was an effective therapy for atrophic post acne scars. Added to it human placental and mesenchymal stem cells mesotherapy augment the efficacy. There was highly significant improvement after treatment in all scar types (Rolling, Ice peak and Boxcar) in both modalities of treatment but microneedling + mesotherapy showed more excellent clinical outcome than microneedling side. Both methods are tolerated regarding short term side effects including pain, burning sensation, erythema and edema in addition to short downtime.

Statistical Analysis

The data was presented as a means standard deviation. Using t-tests, the effectiveness and side effects of the two treatment sides were compared statistically. P values less than 0.05 were considered statistically significant.

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