Received: 28 January 2022 | Accepted: 9 February 2022

DOI: 10.1111/dth.15376

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

Microneedling with topical vitamin C versus microneedling with topical insulin in the treatment of atrophic post-acne scars: A split-face study

Mohamed Ali Mahmoud Abbas[1] | Emad Eldin Abd Elmoneim Elgamal[2] | Mohamed Shokry Zaky[2] | Mohamed L. Elsaie[3]

[1]Department of Medical Physiology, Damietta Faculty of Medicine, Al-Azhar University, Cairo, Egypt

[2]Department of Dermatology, Venereology and Andrology, Damietta Faculty of Medicine, Al-Azhar University, Cairo, Egypt

[3]Department of Dermatology, Medical Research and Clinical Studies Institute, National Research Centre, Cairo, Egypt

Correspondence
Mohamed L. Elsaie, Department of Dermatology, Medical Research and Clinical Studies Institute, National Research Centre, Cairo, Egypt.
Email: egydoc77@yahoo.com

Abstract

Post acne scars following sebaceous injury and abnormal wound healing during the course of acne is a prevalent and challenging to treat condition To evaluate microneedling by dermapen with topical vitamin C versus microneedling with topical insulin in treating atrophic post-acne scars. A split-face comparative study included 30 subjects with atrophic post-acne scars. Human insulin was topically applied to the left side of the face and on the right side, vitamin C serum was applied. Scars were assessed via the Acne Scar Assessment Scale (ASAS) and Scar quartile grading scale (SQGS). After 1 month of 4 treatments, a statistically significant mean improvement in ASAS value was reported on both split sides of the face (2.13 and 1.83) compared to baseline (3.03 and 2.93) ($p = 0.005$; $p = 0.001$ respectively). When compared to baseline, the mean ASAS value improved significantly with a slight more improvement on the vitamin c treated side. Topical insulin and vitamin c combined with microneedling, may both achieve comparable significant improvement for treating post acne scars. Insulin can be a promising novel anti-scarring therapy pending larger controlled studies to verify its efficacy.

KEYWORDS
insulin, microneedling, post-acne scars, vitamin C

1 | INTRODUCTION

Acne is a common chronic inflammatory condition which be complicated by post acne scarring.[1] Numerous methods have been described for the treatment of acne scars, but to date, the optimal treatment method has not been established. A wide variety of treatments have been advocated of which, microneedling has been demonstrated to promote skin remolding by producing hundreds of tiny channels that go from the epidermis to the dermis.[2]

Vitamin C is an antioxidant that when used topically promoted and improved collagen formation by increasing mRNA levels of collagens I and III as well as by increasing levels of tissue inhibitors of matrix metalloproteinase 1.[3]

Insulin, a potent factor of wound healing, has been reported to induce rapid recovery of various wounds. In addition to regulating re-epithelialization and inflammatory responses at wound tissues, insulin also exerts angiogenic effect on wounds. Topical insulin increases collagen formation as well as new blood vessel formation in healing tissues via synthesis of transforming growth factor (TGF-b1) and vascular endothelial growth factor (VEGF).[4]

Recent very few reports demonstrated a potential role for topical insulin in treating scars.[5,6] Given such outlined potential; we aimed to examine the anti scarring effect of topical insulin combined with microneedling against that of topical vitamin C combined with microneedling for post acne scars.

2 | PATIENTS AND METHODS

This comparative clinical experiment used a split face technique on 30 cases with atrophic post-acne scars that were identified clinically based on typical skin lesions. Patients were recruited from Al-Azhar University's Damietta Dermatology outpatient clinic. The study was approved by the Damietta Faculty of Medicine Al-Azhar University's Research Ethics Committee (IRB00012367-21-03-009). After briefing each patient about the processes of the treatment and the expected consequences or probable problems, they signed a written informed consent form.

Facial acne scars and a minimum age of 18 years were both required for inclusion. Pregnant or nursing women, aggressive inflammatory acne, and active infection in the treatment area (e.g., verrucae and herpes simplex), dermatoses, melanoma, or lesions suspected of becoming cancerous (e.g., psoriasis and eczema), systemic disease, anticoagulant therapy (hypertension, diabetes or bleeding tendency) and also history of keloidal tendency were all excluded from the study.

2.1 | Sample size calculation

Using the following calculation, the study's sample size was determined to be (30) individuals at a 5% level of significance and 90% power[7]

$$N = \frac{Z_2 \times P \times (1-P)}{d_2}$$

where; $Z = 1.96$ for 95% confidence level, $P =$ the expected efficacy of micro needling with topical vitamin C versus micro needling with topical insulin in the treatment of post-acne atrophic scars (81%), and $d =$ precision (Margin of error) $= 0.03$.

Thirty cases of atrophic post-acne scars assessed clinically based on normal skin lesions.

3 | METHODS

3.1 | Patient preparation

The subjects face was cleansed using a skin disinfecting product and numbed using a topical anesthetic prior to the treatment. A sterile gel was applied to the subject's face to prevent abrasion and friction during the treatment. Microneedling was carried out with a 36 disposable needle tipped dermapen (Dr. Pen Ultima A6 Professional Microneedling Pen; Bjheyetec Electronic Technology Co., Guangzhou, China) at high-speed mode with a needle length adjusted to 2 mm protrusion. The skin of face was stretched by one hand while the other was used to pass the instrument over in a direction perpendicular to that of stretching force in a vibrating stamp-like manner till pin point bleeding occurs. During the treatment blood was wiped away with a sterile saline solution, to prevent encrustation. Human actrapid insulin 100 IU/ml® solution (Actrapid; Novo Nordisk Pharmaceuticals Ltd, Bagsværd, Denmark) was applied to the left side of the face in 10 units (0.1 ml) and on the right side, 2 ml of vitamin C (17%) was applied. Ice pack was applied over the treated areas and face was cleaned after 30 min. Fucidinic acid ointment was prescribed twice daily and for 5 days post procedure. Adverse effects (AE) were noted and patients were advised to follow photoprotective measures. All the patients received four treatments at monthly interval and were followed up 4 weeks after the last session.

3.2 | Measurement of effectiveness

Digital images of the subject's face were randomized and analyzed independently using the Acne Scar Assessment Scale (ASAS). The ASAS scale is a validated 5-point photo numeric descriptive grading scale used to grade acne scarring ranging from 0 ("Clear") to 4 ("Severe"). Moreover by using the Scar quartile grading scale (SQGS), pre and post procedure digital images were analyzed by an independent blinded dermatologist to determine the degree of improvement, and the outcomes were scored on the basis of the percentage improvement as follows: Grade 0 indicates no progress, Grade 1 indicates less than 25% improvement, Grade 2 indicates 26%–50% improvement, Grade 3 indicates 51%–75% improvement, and Grade 4 indicates greater than 75% improvement.

3.3 | Patient satisfaction

The degree of improvement, in the view of the patients, was assessed. At the last session, the patients were questioned about their level of satisfaction with the outcomes in comparison to the pre-treatment state on both sides and graded by a five point scale as excellent, good, fair, or poor.

3.4 | Statistical analysis

The data was gathered, edited, coded, and put into IBM SPSS version 23 (Statistical Package for Social Science). When the quantitative data distribution was judged to be parametric, mean and standard deviations were provided, but data with non-parametric distributions were presented as median with inter-quartile ranges (IQR). To indicate qualitative features, numbers and percentages were also used.

4 | RESULTS

In current study, mean age of subjects was 26.73 ± 4.76 years. Seven, 7/30 (23.3%) of subjects were males and the mean duration of the scar was 5.9 ± 2.29 years. Twelve, 12/30 (40%) subjects had boxcar

scars while eight, 8/30 (26.7%) of subjects presented with either icepick or rolling scars (Table 1).

After 1 month of four treatments, a statistically significant mean improvement in ASAS value was reported on both split sides of the face (2.13 and 1.83) compared to baseline (3.03 and 2.93) ($p = 0.005$; $p = 0.001$ respectively). When compared to baseline, the mean ASAS value improved significantly with a slight more improvement on the vitamin c treated side (Tables 2 and 3).

Another assessment parameter used was SQGS on the right half, 13 patients showed more than >75% improvement, 7 patients showed 51–75% improvement, 4 patients showed 26%–50% improvement, 4 patients showed <25% improvement whereas on the left half >75% improvement was seen in 1 patients, 51%–75% improvement in 6 patients, 26%–50% improvement in 9 patients, <25% improvement in 8 patients. Overall improvement was more significant on the vitamin C treated side ($p = 0.0036$) (Table 4; Figure 1).

Subjects also assessed their acne scarring compared to baseline using a four grade Likert scale (poor, fair, good or excellent). Fourteen, 14/30 (46.7%) of subjects reported excellent satisfaction with their acne scarring on the right (vitamin c treated) side while only two, 2/30 (6.7%) reported excellent satisfaction on the left (insulin-treated) side. Nine subjects 9/30 (30%) reported a poor outcome on the left (insulin treated) side. Satisfaction of patients was significantly more with vitamin C treated (right) side compared to the insulin treated (left) side ($p < 0.001$) (Table 5).

No serious adverse events were reported. The most common side effect reported was edema followed by erythema. There was no difference in side effects observed on either side ($p = 0.97$). No adverse events persisted at the final follow up (Table 6).

TABLE 1 Demographic data of the studied subjects

Variables	Studied cases
Age (years)	26.73 ± 4.76
Sex	
Male	7 (23.3%)
Female	23 (76.7%)
Acne duration (years)	5.9 ± 2.29
Type of acne lesion	
Icepick	8 (26.7%)
Boxcar	12 (40.0%)
Rolling	8 (26.7%)
Mixed	2 (6.6%)

5 | DISCUSSION

Microneedling treatments can pose a safe and effective option in the reduction of acne scarring. In this study, microneedling helped achieving a significant reduction of acne scars while showing high patient safety.[8] A plethora of recent studies revealed that microneedling can

TABLE 2 Acne Scar Assessment Scale before treatment of the studied cases

Grade	Right side no. (%)	Left side no. (%)	Test significance	*p* value
1 (very mild)	2 (0.0%)	0 (0.0%)	4.28	0.23
2 (mild)	7 (26.7%)	9 (30.0%)		
3 (moderate)	12 (43.3%)	11 (36.7%)		
4 (severe)	9 (30.0%)	10 (33.3%)		
Mean ± SD	2.93 ± 0.62	3.03 ± 0.82		

Note: *p*-value >0.05: Non significant; *p*-value <0.05.

TABLE 3 Acne Scar Assessment Scale before and after treatment of the studied cases regarding right and left side

		Before		After			
	Grade	No	%	No	%	Test significance	*p* value
Grading in right side (Vitamin C)	1 (very mild)	2	0.0%	12	40.0%	17.98	0.001*
	2 (mild)	7	26.7%	11	36.7%		
	3 (moderate)	12	43.3%	7	23.3%		
	4 (severe)	9	30.0%	0	0.0%		
	Mean ± SD	2.93 ± 0.62		1.83 ± 0.27			
Grading in left side(Insulin)	1 (very mild)	0	0.0%	7	23.3%	12.78	0.005*
	2 (mild)	9	30.0%	13	43.3%		
	3 (moderate)	11	36.7%	9	30.0%		
	4 (severe)	10	33.3%	1	3.3%		
	Mean ± SD	3.03 ± 0.82		2.13 ± 0.35			

Note: *p*-value >0.05: Non significant; *p*-value <0.05.
*Statistically significant.

TABLE 4 Scar quartile grading scale degree of improvement

Improvement grade	Microneedling with vitamin C *n* (%)	Microneedling with topical insulin *n* (%)	Test significance	*p* value
Grade 0	2 (6.7%)	6 (20.0%)	15.62	0.0036*
Grade 1	4 (13.3%)	8 (26.7%)		
Grade 2	4 (13.3%)	9 (30.0%)		
Grade 3	7 (23.3%)	6 (20.0%)		
Grade 4	13 (43.3%)	1 (3.3%)		

Note: *p*-value >0.05: Non significant; *p*-value <0.05.
*Statistically significant

FIGURE 1 Male patient 32 years old showed (1) right side of the face (Vit C) before treatment, (2) right side of the face (Vit C) 1 month after last session of treatment (3) Left side of the face (insulin) before microneedling (4) left side of the face (insulin) 1 month after last session treatment

provide significant improvements of acne scars, regardless of severity (mild–severe) at baseline, scar type (global, icepick, rolling, boxcar).[9–11] Amelioration in skin by microneedling was related to promoting neocollagenesis as well as to modulation of gene expression in treated skin, inducing skin repair.[12]

Vitamin C improves and promotes tissue repair and neocollagenesis. It acts as a co-factor for the proline and lysine hydroxylases that stabilize the collagen molecule tertiary structure, and it also promotes collagen gene expression.[13] Two previous studies revealed excellent improvement in acne scars with topical application of vitamin c preceded by microneedling.[14,15]

The role of topical insulin in wound healing has been under scrutiny in literature since 1960's and 1970's.[16,17] Various studies have been done in animal models and humans and it has been found that topical Insulin therapy exerts its effects via IGF 1 receptor. The use of topical insulin in diabetic foot has shown to produce faster epithelization rates.[18] Insulin has been known to stimulate keratinocytes and the rate of endothelial proliferation leading to faster neovascularization and formation of granulation tissue.[19] However, its effect on scarring has only recently come under review through investigating efficacy of a single dose of insulin in the prevention of excessive cutaneous scarring in breast surgery patients demonstrated that subcutaneous insulin injections reduced the appearance of scarring in this study compared with placebo.[20] Another recent study demonstrated that intralesional injection or topical spraying of insulin prevented the development of hypertrohic scars (HS) following wound injuries in susceptible patients.[5]

TABLE 5 Patient satisfaction of the studied cases regarding right and left side

Variables	Right side (Vitamin C)	Left side (Insulin)	Test significance	*p* value
Poor	3 (10.0%)	9 (30.0%)	18.33	<0.001*
Fair	5 (16.7%)	15 (50.0%)		
Good	8 (26.7%)	4 (13.3%)		
Excellent	14 (46.7%)	2 (6.7%)		

Note: *p*-value >0.05: Non significant; *p*-value <0.05.
*Statistically significant.

TABLE 6 Side effect on both split sides during treatments

Side effects	Microneedling with vitamin C *n* (%)	Microneedling with topical insulin *n* (%)	Test significance	*p* value
Erythema	2 (6.7%)	2 (6.7%)	0.53	0.97
Edema	4 (13.3%)	4 (13.3%)		
Infection	4 (13.3%)	4 (13.3%)		
Hyper-pigmentation	2 (6.7%)	1 (3.3%)		
Pain	2 (6.7%)	3 (10.0%)		

Note: *p*-value >0.05: Non significant; *p*-value <0.05.

Only one study reported the application of topical insulin on acne scars following microneeedling. In their study, Pawar and Singh, investigated the administration of either topical platelet-rich plasma (PRP) or topical fast-acting insulin (40 IU/ml of human insulin and 0.3% metacresol) for the treatment of postacne atrophic scars and concluded that microneedling with topical insulin or PRP was associated with statistically significant improvement in postacne atrophic scar.[6]

Topical insulin had been shown to improve and promote wound healing when applied topically by regulation inflammatory response and decreasing tissue levels of reactive oxygen species (ROS).[21] Moreover, topical insulin application for wounds had been shown to eliminate dead tissues by recruiting neutrophils and facilitating chemotaxis and phagocytosis of macrophages.[22]

Limitations include the small sample, size and the absence of a control group consisting of microneedling alone that could have given better comparison. The patients had been followed up for only 4 weeks post treatment which is relatively short.

In conclusion, we have demonstrated that both topical Vitamin C and topical insulin combined with microneedling may achieve comparable significant improvement. The good safety profile, easy accessibility, low cost, and non-invasive nature merits the use of both topical medications. Insulin can be a promising novel anti-scarring therapyalthough more work is required to more precisely delineate who is likely to benefit from treatment as well as to which delivery form of the insulin formulation would be optimal.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest

AUTHOR CONTRIBUTIONS

All authors contributed equally in producing the work. Mohamed Ali Mahmoud Abbas, Emad Eldin Abd Elmoneim Elgamal, Mohamed Shokry Zaky, and Mohamed L. Elsaie designed and performed the research. Mohamed Ali Mahmoud Abbas, Emad Eldin Abd Elmoneim Elgamal, Mohamed Shokry Zaky, and Mohamed L. Elsaie performed the work. Mohamed Ali Mahmoud Abbas, Emad Eldin Abd Elmoneim Elgamal, Mohamed Shokry Zaky, and Mohamed L. Elsaie analyzed and wrote the paper.

DATA AVAILABILITY STATEMENT

Data are available upon request from contact author.

ORCID

Mohamed L. Elsaie https://orcid.org/0000-0001-7541-5241

REFERENCES

1. Mohamed EE, Tawfik K, Elsaie M. Intense pulsed light versus 1,064 long-pulsed neodymium: yttrium-aluminum-garnet laser in the treatment of facial acne vulgaris. *J Clin Diagn Res*. 2016;10(7):WC01-WC03. doi:10.7860/JCDR
2. Gupta A, Kaur M, Patra S, Khunger N, Gupta S. Evidence-based surgical management of post-acne scarring in skin of color. *J Cutan Aesthet Surg*. 2020;13(2):124-141.
3. Pinnell SR, Yang H, Omar M, et al. Topical L-ascorbic acid: percutaneous absorption studies. *Dermatol Surg*. 2001;27(2):137-142.
4. Liu Y, Dhall S, Castro A, Chan A, Alamat R, Martins-Green M. Insulin regulates multiple signaling pathways leading to monocyte/macrophage chemotaxis into the wound tissue. *Biol Open*. 2018;7:1. doi:10.1242/bio.026187
5. Reddy C, Chittoria RK, Aggrawal A, et al. Role of insulin in prevention of hypertrophic scars. *Adv Pharmacol Clin Trials*. 2020;5(1):000173.
6. Pawar M, Singh M. Microneedling with autologous platelet-rich plasma versus microneedling with topical insulin in the treatment of postacne atrophic scars: a simultaneous split-face comparative study. *J Am Acad Dermatol*. 2021;84(3):810-811.
7. Daniel WW. *Biostatistics: A Foundation for Analysis in the Health Sciences*. 7th ed. John Wiley & Sons; 1999.
8. Casabona G, Alfertshofer MG, Kaye KO, et al. Safety and efficacy of microneedling technology in the treatment of acne scars. *J Cosmet Dermatol*. 2021;20(11):3482-3491.

9. Juhasz MLW, Cohen JL. Microneedling for the treatment of scars: an update for clinicians. *Clin Cosmet Investig Dermatol*. 2020;13:997-1003.
10. Tirmizi SS, Iqbal T, Mansoor M, et al. Role of microneedling in atrophic post-acne scars: an experience from a tertiary care hospital. *Cureus*. 2021;13(1):e12578.
11. Elsaie ML. Update on management of keloid and hypertrophic scars: a systemic review. *J Cosmet Dermatol*. 2021;20(9):2729-2738.
12. Zeitter S, Sikora Z, Jahn S, et al. Microneedling: matching the results of medical needling and repetitive treatments to maximize potential for skin regeneration. *Burns*. 2014;40(5):966-973.
13. Ivanov V, Ivanova S, Kalinovsky T, Niedzwiecki A, Rath M. Inhibition of collagen synthesis by select calcium and sodium channel blockers can be mitigated by ascorbic acid and ascorbyl palmitate. *Am J Cardiovasc Dis*. 2016;6(2):26-35.
14. Chawla S. Split face comparative study of microneedling with PRP versus microneedling with vitamin C in treating atrophic post acne scars. *J Cutan Aesthet Surg*. 2014;7(4):209-212. doi:10.4103/0974-2077.150742. Erratum in: *J Cutan Aesthet Surg*. 2015;8(1):75.
15. Essameldin AN, Abdo RS, Mostafa MA, Mohhmed RI. Efficacy of microneedling with topical vitamin C in treatment of acne scars. *Sohag Med J*. 2018;22(1):163-170.
16. Paul TN. Treatment by local application of insulin of an infected wound in a diabetic. *Lancet (London, England)*. 1966;2(7463):574-576.
17. Belfield WO, Golinsky S, Compton MD. The use of insulin in open-wound healing. *Vet Med Small Anim Clin*. 1970;65(5):455-460.
18. Scimeca CL, Bharara M, Fisher TK, Kimbriel H, Mills JL, Armstrong DG. Novel use of insulin in continuous-instillation negative pressure wound therapy as "wound chemotherapy". *J Diabetes Sci Technol*. 2010;4(4):820-824.
19. Stephen S, Agnihotri M, Kaur S. A randomized controlled trial to assess the effect of topical insulin versus normal saline in pressure ulcer healing. *Ostomy Wound Manage*. 2016;62(6):16-23.
20. Hallam MJ, Pitt E, Thomas A, Nduka C. Low-dose insulin as an Anti-scarring therapy in breast surgery: a randomized controlled trial. *Plast Reconstr Surg*. 2018;141(4):476e-485e.
21. Wang J, Xu J. Effects of topical insulin on wound healing: a review of animal and human evidences. *Diabetes Metab Syndr Obes*. 2020;13:719-727.
22. Chen X, Liu Y, Zhang X. Topical insulin application improves healing by regulating the wound inflammatory response. *Wound Repair Regener*. 2012;20(3):425-434.

How to cite this article: Abbas MAM, Elgamal EEAE, Zaky MS, Elsaie ML. Microneedling with topical vitamin C versus microneedling with topical insulin in the treatment of atrophic post-acne scars: A split-face study. *Dermatologic Therapy*. 2022;35(5):e15376. doi:10.1111/dth.15376