

RESEARCH ARTICLE

The Therapeutic Efficacy of Microneedling Combined with Topical Tacrolimus vs. Microneedling Alone in Treatment of Stable Vitiligo. A Comparative Study.

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Received: 28th Jan, 2020; Revised: 10th Feb, 2020; Accepted: 20th Mar, 2020; Available Online: 25th Mar, 2020

ABSTRACT

Background: Vitiligo is an acquired depigmentary disorder of multifactorial etiology. Several treatment modalities have been attempted with partial success, but the recent focus on surgical treatment like micro-needling.

Objective: To compare the safety and ability of micro-needling alone in the induction of pigmentation in stable vitiligo versus combined tacrolimus treatment and micro-needling.

Patients and methods: Twenty three patients with stable vitiligo were recruited from the Department of Dermatology and Venereology of Salah Aldeen General Hospital. The patients then subjected to micro-needling of the two vitiliginous patches after that application of topical tacrolimus to the left patch. This procedure was repeated every two weeks for a maximum of 5 months (10 sessions).

Results: Microneedling with topical tacrolimus showed better but non-significant response than micro-needling alone (p = 0.519). Moderate improvement occurred in 13% of patches treated with micro-needling alone, while only 9% show moderate improvement in combined treatment. Although 9% show good improvement in combined treatment.

Conclusion: Micro-needling induces pigmentation in vitiligo patients, and the addition of topical tacrolimus induces a better response. However, no statistically significant response was observed in any group.

Keywords: Micro-needling, Tacrolimus, Vitiligo.

International Journal of Pharmaceutical Quality Assurance (2020); DOI: 10.25258/ijpqa.11.1.16

How to cite this article: Ahmed AA, Dahash MA, Fateh DM, Najim WS. The Therapeutic Efficacy of Microneedling Combined with Topical Tacrolimus vs. Microneedling Alone in Treatment of Stable Vitiligo. A Comparative Study. International Journal of Pharmaceutical Quality Assurance. 2020;11(1):109-115.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Vitiligo is acquired and inherited depigmentary skin disorder. It occurs secondary to the selective destruction of melanocytes by the body's immune system.^{1,2} It was characterized by well-circumscribed, chalky white or milky macules or patches.^{3,4} In the United States, 'vitiligo occurs in about 1% of the population.^{5,6} The goal of vitiligo treatment is to regulate the response damage to melanocytes and stimulate their migration from close skin and body part reservoirs. Treatment is also divided into medical specialty, surgical and physical, which can sometimes be combined.⁷ Calcineurin inhibitors are immune-suppressants, the first of which, cyclosporine, is not used topically due to the lack of good cutaneous absorption. Subsequently, tacrolimus and pimecrolimus, and other calcineurin inhibitors, demonstrated good absorption when used topically.⁸ Topical tacrolimus

is a calcineurin inhibitor that controls the activity of T lymphocytes through the inhibition of unhealthy cytokines, blocking the transcription of the interleukin-2 (IL-2) genes which are important for the proliferation of cytotoxic T lymphocytes, and also inhibiting the transcription and production of IL-4, IL- 5, IL-10, IFN- γ , and TNF- α .⁹

Microneedling (MN) or needle of the skin, is an aesthetic technique that has been used for decades before laser re-shows but has recently seen a surge in popularity, especially for ethnic skin. In 1995, acupuncture or skin was identified by the effective treatment of scars. Since then, the technique initially referred to as inflammatory collagen therapy has become an essential element in the treatment of acne scars, surgical scars, photoaging, and stretch marks.¹⁰ The needle-needle technique involves the use of sterile needles, 0.1 mm to 2.5 mm long, that penetrate the corneal layer repeatedly

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and produce microscopic “holes” in the dermis, which in turn induces wound healing. These microscopic lesions lead to the release of growth factors, such as platelet-derived growth factors (PDGF), transforming growth factor- α (TGF- α), and transforming growth factor- β (TGF- β) that stimulate the formation of new collagen, elastin in the dermis.¹¹ There are many brands and manufacturers of micro-needling tools on the market, including derma rollers, derma pen, derma stamp, Cosmopen, and many other devices in the office and home.¹² Dermaroller is a cylindrical roller covered with solid steel medical grade microneedles (192 micro-needles), arranged in 24 circular arrays; each array consists of 8 micro-needles. The depth of needle penetration ranges from 0.5–1.5mm.^{13,14} Dermapen is an automatic electrically powered pen-like MN device that use disposable needles. The length of the needles can be adjusted according to the site. The disposable tip has 9–12 needles. It works in a vibrating stamp-like manner.¹⁵

Micro-needling has been effectively used for drug delivery and for treating many skin conditions and diseases. Micro-needling is considered a safe and effective in-office procedure with a range of uses. Many new indications are currently being explored. In many practices, have used micro-needling for atrophic scars, repigmentation of depigmented scars and vitiligo, stimulation of hair regrowth in noninflammatory alopecias, and treatment of burn scars. Patients are generally very happy with the quick treatment time, minimal downtime, and overall long-term results.¹⁶

PATIENTS AND METHODS

This study is a treatment trial study conducted on 23 patients of stable vitiligo that unresponsive to medical treatment or phototherapy. The sample was recruited from the Department of Dermatology and Venereology, Salah Aldin General Hospital, during the period from November 2018 to May 2019. Informed consent was obtained from patients. Micro-needling of two contralateral vitiliginous patches of vitiligo was performed with a derma pen, then the application of tacrolimus on the left patch in each patient.

Method

Each patch was anesthetized with local anesthesia (EMLA; 2.5%prilocaine + 2.5%lidocaine) for 30 minutes then sterilized using a sterile gauze soaked with povidone-iodine solution. The patients then subjected to micro-needling of the two vitiliginous patches with derma pen (My M Microneedle Therapy, Guangzhou, China) after that tacrolimus 0.1% (fingerprint per 1 cm²) was applied to the left patch in each patient under an occlusive dressing. At the same time, the right patch was treated with micro-needling alone. The patients then advised to apply topical tacrolimus once daily over the left patch in each patient. This procedure was repeated every two weeks for a maximum of 5 months (10 sessions).

Intervention

Microneedling using the derma pen of the two patches had been done until pinpoint bleeding appeared, then topical

tacrolimus ointment was applied (fingerprint per 1 cm²) to the left one.

The micro-needling technique was done from 2 mm outside the borders of patches toward the center until pinpoint bleeding appeared in each patch.

Evaluation of Treatment

The evaluation was made with pre and post-treatment clinical photographs using Canon camera with 14 megapixels. Patients also assessed the percentage of repigmentation achieved on subjective assessment scale of 0-4 (0: no improvement; 1: 1–25% mild improvement; 2: 26–50% moderate improvement; 3: 51-75% good improvement; 4: 76-100% excellent improvement).

Statistical Analysis

Data was translated into a computerized database structure. Statistical analysis was done using SPSS (Statistical Package for Social Sciences). Version 20 computer software. Categorical variables were presented as frequency and percentage. Chi-square was used to test the significance of the association between categorical variables with considered P. Value of ≤ 0.05 was statistically significant.

RESULTS

A total of 23 patients with vitiligo were enrolled in this study, their ages ranged from 14–57 years with mean \pm SD years 24.8 ± 12.4 , (60.9%) of them were under 20 and (39.1%) were over 20 years old. Regarding gender, the results showed the ratio of female more than male as (57 and 43% respectively) and without any significant association between age and sex ($p = 0.637$) as shown in Figure 3.1 and Tables 3.1 and 3.2)

Regarding the clinical types of vitiligo, the result showed 16 (69.6%) of patients with generalized type, acral type 6 (26.1%), and segmental vitiligo 1(4.3%). The distribution of the duration of vitiligo and sites of vitiliginous lesions are shown in Table 3.3 and Figure 3.2.

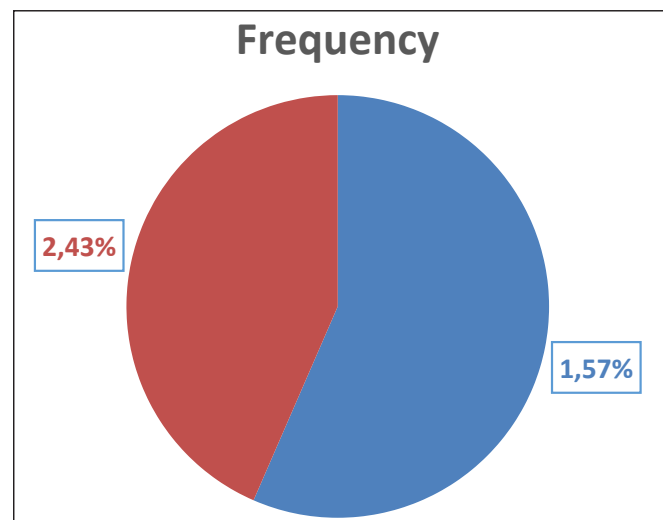


Figure 3.1: Distribution of Study Sample According to Sex. N = 23

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Table 3.1: Frequency of study sample regarding the age and the sex

Age	Frequency	Percent
>20	14	60.9
< 20	9	39.1
Total	23	100

Sex	Frequency	Percent
f	13	56.5
m	10	43.5
Total	23	100

Table 3.2: Relationship between age and sex. n = 23

		Age		Total
		>20	< 20	
Sex	f	8	5	13
	m	6	4	10
Total	14	9	23	

Fisher s Exact Test 1.000 p = 0.637

Table 3.4: Distribution of study sample according to family history

Family history		Frequency	Percent
-ve		15	65.2
+ve		8	34.8
Total		23	100.0

Table 3.3: Distribution of study sample according to disease characteristic. N = 23

Types		Frequency	Percent
Types	Generalized	16	69.6
	Acral	6	26.1
	Segmental	1	4.3
	Total	23	100.0

Duration		Frequency	Percent
Duration	<5 years	10	43.5
	>5 years	13	56.5
	Total	23	100.0

Site		Frequency	Percent
Site	Hand	10	43.5
	Face	2	8.7
	Forearm	4	17.4
	Leg	1	4.3
	Foot	3	13.0
	Trunk	3	13.0
	Total	23	100.0

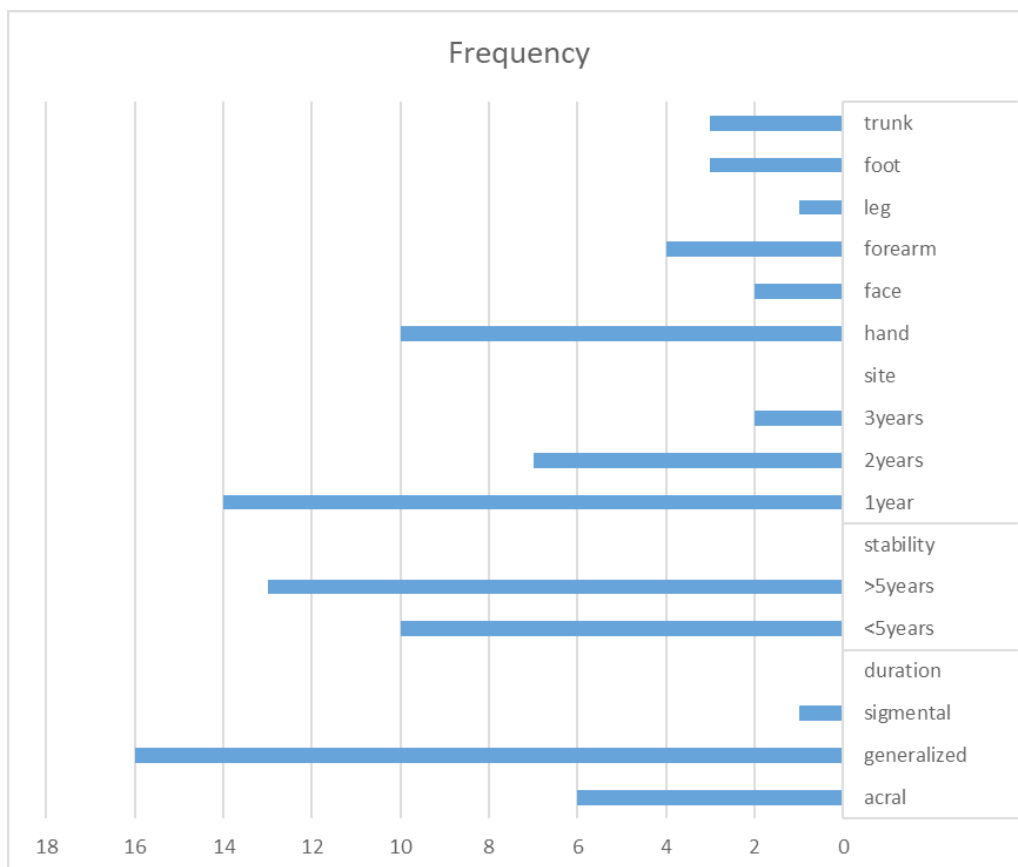


Figure 3.2: Distribution of Study Sample according to Characteristic of Disease. n = 23

The result of the study showed more than 65% of the cases with negative family history, and nearly 34.8% had a positive family history of vitiligo, as shown in Table 3.4.

Regarding the therapeutic response, final results were confirmed by the percentage of repigmentation seen after 5 months of the treatment trial, in which the percentages of

repigmentation with micro-needling and topical tacrolimus ointment were comparable to micro-needling alone, with no statistical difference ($p = 0.519$) between them. Although the left side patch showed slightly more responsive, without a statistical difference as shown in Table 3.5 and Figure 3.3.

Table 3.6: The relation between types and response

	Group		Response				Total	p-value
	0	1	2	3				
Right Side (M)	Types	Generalized	3	10	3		16	0.105 Df= 4 6.583
		Acral	4	2	0		6	
		Segmental	1	0	0		1	
	Total	8	12	3	23			
Left Side (M+T)	Types	Generalized	3	9	2	2	16	0.459 Df=4 5.394
		Acral	3	3	0	0	6	
		Segmental	1	0	0	0	1	
	Total	7	12	2	23			

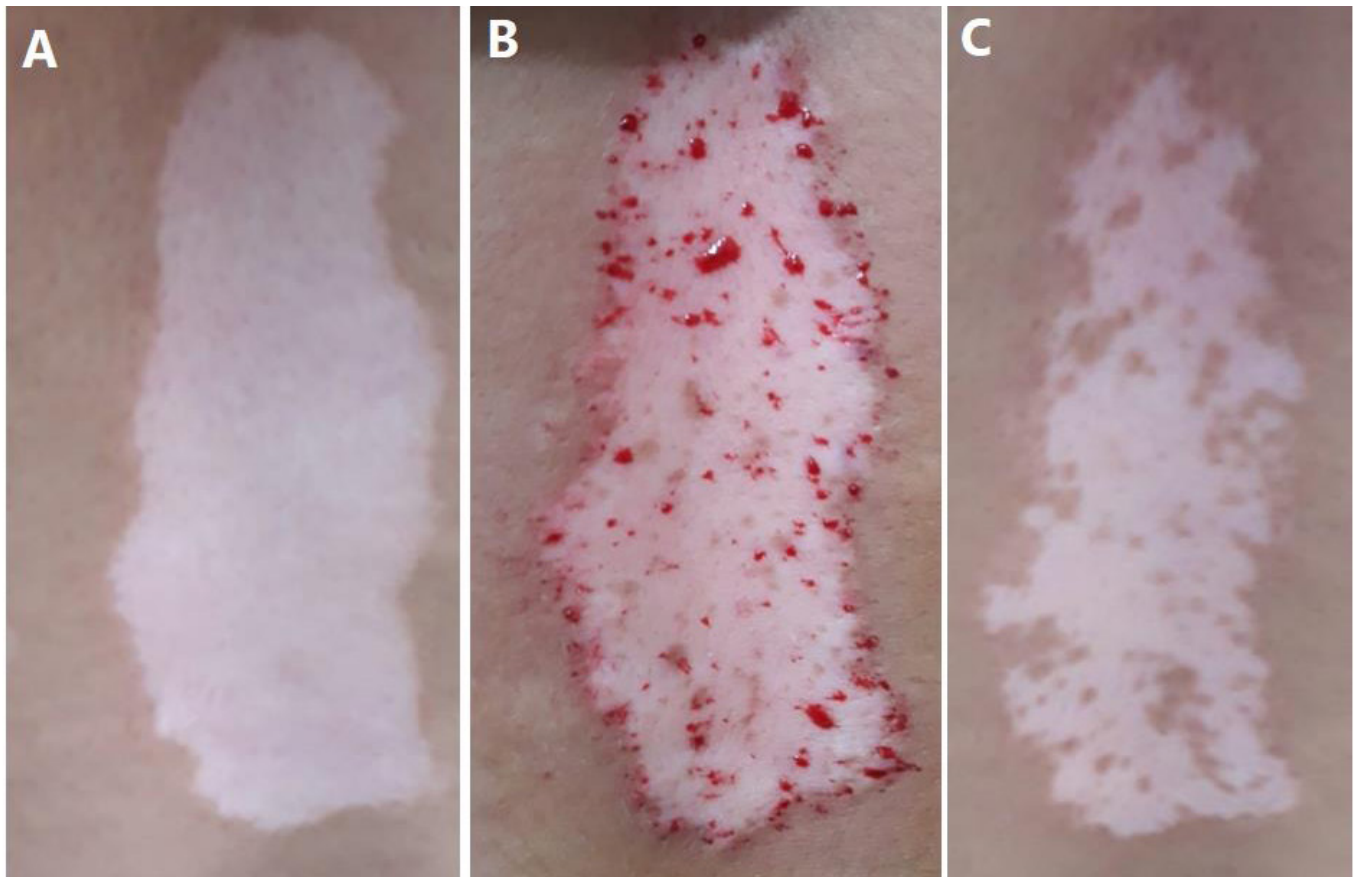


Figure 3.3: 23 years old Man with lower back patch Before Treatment (A), Pinpoint Bleeding after Microneedling Alone (B), after Ten Sessions (C).

Table 3.5: Relationship of therapeutic response between the two Sides

Response		Group		Total no. of patches
		Right side (M)	Left side (M+T)	
0	8 (34.78%)	7 (30.43%)	15	
1	12 (52.17%)	12 (52.17%)	24	
2	3 (13.04%)	2 (8.69%)	5	
3	0 (0%)	2 (8.69%)	2	
Total	23	23	46	

Peasron Chi-square 2.267 3 df = 0.519
 Percentage of repigmentation: 0 = no repigmentation, 1 = 1–25% repigmentation, 2 = 26–50% repigmentation, 3 = > 50% repigmentation, M = Microneedling. M+T = microneedling+ tacrolimus ointment.

Percentage of repigmentation: 0 = no repigmentation, 1 = 1–25% repigmentation, 2 = 26–50% repigmentation, 3 = > 50% repigmentation, M = microneedling. M+T = microneedling+ tacrolimus ointment.

Figure 3.3: 23 years old Man with lower back patch Before Treatment (A), Pinpoint Bleeding after Microneedling Alone (B), after Ten Sessions (C).

Finally, generalized type of vitiligo showed more response than other types in both groups of treatment (Right and Left), but without any significant difference in the two groups (p = 0.105 and p = 0.459 respectively) as shown in Table 3.6.

DISCUSSION

Vitiligo is a skin disease of spontaneous depigmentation characterized by white patches on different areas of the body.^{17,18} Vitiligo is caused by the skin- and hair-follicle melanin depigmentation, but the pathogenesis remains unclear.¹⁹ About 1–2% of people are affected by vitiligo globally, with no predilection for age, sex, or race.²⁰ This disease is easy to diagnose, but few treatments are available, and patient quality of life is often negatively affected.²¹ Many medical treatments have been attempted with partial success, but recent focus has been on surgical techniques. This study aimed to evaluate and compare the therapeutic efficacy of micro-needling and micro-needling combined with topical tacrolimus ointment in the management of localized stable vitiligo. This is the first study used micro-needling for treatment of Vitiligo in Iraq, Although the idea of combining therapy is not a new approach for the treatment of vitiligo, many trials have shown that compound therapies improve overall efficacy and time to achieve pigmentation that reduces possible side effects. Microneedling therapy is advantageous because it is an in-office treatment, which ensures patient adherence to therapy. In addition, it offers no

systemic side effects that might complicate treatment when using oral medications.

The result showed that micro-needling modality has the ability in the induction of pigmentation in stable localized vitiligo patients. And this finding representing a starting point for further working in this field.

In the study, we observed most of our patients 65.2% in the right side group (represent micro-needling alone treated patch) shows variable improvements despite the short duration of the study and our strict inclusion criteria like patients previously unresponsive to medical treatment or phototherapy,

So the result of study shows the response of patients to treatment was different according to procedure types (Micro-needling and topical tacrolimus ointment) or (micro-needling only). However, the response to treatment was more effective in combination method (70%) than those treated by micro-needling alone (65%) but without a statistical difference (p = 0.519).

This result was similar to the study conducted in the Department of Dermatology and Venereology, University of Tanta in Egypt (2017)²² that found the pigmentation began in 56% of the patches treated with tacrolimus along with micro-needling after 4 Sessions (within 6 weeks).while another study conducted in Kerman, Iran (2009)²³ that found 25.7% of the patches showed Start pigmentation one month after the end of the course treatment (10 sessions).

This can be explained by the fact that micro-needling device produced pores thin vertical skin up to 0.5 mm in mid dermis create small skin imperfections that allow the delivery of topical medication to melanocytes in the basal cell layer.²⁴

The present study showed the degree of response more in combination treatment (9% good response and 9% moderate response), but in patients who treat by micro-needling methods were only (13% moderate response).

In Egypt²² study was 40% of patients showed good to excellent response (repigmentation >50%) with tacrolimus combined with micro-needling. These results were close to the results of combination of 5-fluorouracil with dermabrasions which had been studied by Sethi et al,²⁵ who found marked repigmentation (repigmentation >50%) in 56.7% of patients at 4 months.

In India (2018).²⁶ a study was conducted in a tertiary hospital and selected about 50 patients in the age group of 10–50 years who had been taking treatment for vitiligo without much improvement. Needling was done with 5-fluorouracil application over vitiligo patches. After about 1 month of this procedure, they noticed an improvement in about 40% of patients with some erythema and hyperpigmentation developing on the margins of vitiligo patches.

Gradually more than 50% of patients had similar improvement by the end of 2 months. After 3 months, about 60% of patients had hyperpigmentation in the vitiligo lesions with almost complete pigmentation in very small patches; larger ones had less pigmentation and 40% did not have any pigmentation from the previous state.

In a study by Stanimirovic et al. repigmentation of patients with resistant bilateral symmetrical vitiligo by comparing treatment with narrowband ultraviolet B and topical 0.005% latanoprost solution with and without Dermaroller was investigated. Repigmentation was observed in 37.8% of treated lesions and only 8.8% of repigmenting lesions had greater than 50% repigmentation. However, there was no statistically significant difference in repigmentation between groups.²⁷

In a case report by Zawar VP et al.²⁸ in India for patient had stable vitiligo on her left leg for 4 years that was treated by Needling was considered, with topical EMLA cream, and surgical cleaning was done. A 20-gauge needle was inserted at an angle of 45 degrees into pigmented skin over the rim of a vitiligo patch and then moved gradually toward the depigmented zone with multiple insertions all over the patch until pinpoint bleeding occurred. They observed improved peripheral and perifollicular pigmentation in the patch after the first sitting, which gradually showed excellent repigmentation after three sittings done 2 weeks apart.

The supposed mechanisms responsible for repigmentation after needling include trauma-induced inflammation inciting migration of keratinocytes along with melanocytes during healing phase, influx of cytokines and growth factors (e.g. TGF- α , TGF- β and PDGF) leading to stimulation of melanocytes in the periphery of the patch or outer root sheath of pigmented hair, and mechanical migration of melanocytes from pigmented borders to depigmented area. Needling is a simple and safe procedure that may augment repigmentation in unresponsive or sluggishly responding to stable vitiligo. It may be worth trying as an alone modality or as an adjuvant to other therapies.²⁹⁻³¹

CONCLUSION

1. Micro-needling can induce pigmentation in stable vitiligo patients.
2. The addition of topical tacrolimus induces a better response than micro-needling alone. However, no statistically significant response was observed in any group.
3. Micro-needling is a safe and relatively inexpensive method of treatment.

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