Efficacy of topical 5-fluorouracil with microneedling versus topical latanoprost with microneedling in treatment of patients with localized stable vitiligo: A randomized clinical trial

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Abstract

Background: Although several studies were conducted on treatment of localized vitiligo with multiple adjuvants, there is no ideal therapy with optimum results.

Objectives: The purpose of this research is to compare the effectiveness of topical 5-fluorouracil and topical latanoprost in stimulating skin regimentation in patients with localized stable vitiligo following skin microneedling.

Patients and methods: This prospective randomized clinical trial conducted on forty patients with localized stable vitiligo was divided randomly into two groups: Group (A): 20 patients were received latanoprost after microneedling Group (B): 20 patients were received 5-Flourouracil 5% solution after microneedling. All patients were clinically and photographically evaluated using Vitiligo Area Scoring Index (VASI).

Results: There was no statistically significant difference between both groups regarding the degree of repigmentation in response to treatment (p value = 0.317). Excellent improvement (> 75% repigmentation) was achieved in 45% of patients in both groups. Also, there was significant reduction in the VASI score for both groups when comparing post-treatment with the baseline. As regard the complications, there was minimal complications only one case with post inflammatory hyperpigmentation.

Conclusion: Microneedling combined with 5-Fluorouracil or latanoprost are both safe and effective treatments of localized stable vitiligo with no significant difference.

Keywords: Latanoprost; 5-fluorouracil; Microneedling; Vitiligo.

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Introduction

Vitiligo is a pigmentary disorder that affect both sexes and all races and has an erratic and unpredictable course **(Bae et al., 2017)**.It is characterized by selective loss of melanocytes, which is sometimes brushed off as a cosmetic issue despite the fact that its effects can be emotionally distressing and have a significant impact on everyday life **(Bergqvist & Ezzedine, 2020)**. There are currently several techniques accessible to help battle for a better skin appearance due to the fact that vitiligo can be a serious cosmetic issue for sufferers **(Frączek et al., 2022).**

Microneedling is a minimally invasive procedure now used for multiple dermatologic conditions including vitiligo, which considered a safe and effective technique in treatment of vitiligo either alone or combined with other treatments such as topical 5-Flourouracil, latanoprost, tacrolimus or triamcinolone acetonide solution **(Salloum et al., 2020).**

5-Flourouracil is an antimetabolite with antimitotic activity, surprisingly used in vitiligo repigmentation which is a process needs melanocyte proliferation. This was firstly introduced by Tsuji and Hamada in 1983 **(Tsuji & Hamada, 1983)**. It was suggested that the inflammatory reaction due to 5-FU application generates mediators as metalloproteinases that stimulate and facilitate melanocyte proliferation and migration, also it was found that melanocytes are less vulnerable to 5-FU than keratinocytes that undergo selective destruction while melanocytes continue to function **(Gauthier et al., 2013)**.

Latanoprost is a prostaglandin F2 alpha (PGF2) analogue, topical ophthalmic medication used to treat glaucoma by lowering intraocular pressure and brought to attention in vitiligo treatment due to its effect of hyperpigmentation of the iris, eyelashes, and periocular skin**.** The effectiveness of Latanoprost in vitiligo repigmentation was previously studied, and it was found due to enhanced melanin synthesis in response to direct melanocyte stimulation by increased tyrosinase activity **(Nowroozpoor Dailami et al., 2020)**.

The objective of this study is to evaluate and compare the effectiveness of topical application of 5-fluorouracil and topical application of latanoprost following skin microneedling in promoting skin repigmentation in individuals with localized stable vitiligo.

Patient and methods

This a prospective randomized clinical trial was conducted at the outpatient clinic of Dermatology, Venerology and andrology, South Valley University Hospital, throughout the period from Marsh 2022 until December 2022 and included 40 patients with localized stable vitiligo between ages of 10 to 60 years old, did not have any increase or decrease in size, number or pigmentation for at least 3 months, nor history of koebnerization and did not receive any local or systemic medication for at least 3 months. All patients were subjected to full history taking, general and dermatological examination.

This study was approved by Qena Faculty of Medicine institutional ethical committee, registration number (370/3/22), All Patients provided written informed consent before participating in the research, and all candidates were guaranteed confidentiality. A written consent was obtained and signed by every subject in the study for agreement to publish study data, including photos and other materials. The study was registered at clinical trial.com (Identifier: NCT05513924).

Methodology

I. History and clinical examination

1. Comprehensive medical history and disease specifics, including initiation, progression, duration (yearly), location and quantity of lesions, prior treatment, and familial predisposition to vitiligo or other autoimmune disorders.
2. Full clinical examination and adequate dermatologic examination with special consideration to skin Fitzpatrick phototypes(I, II, III, IV, V And VI), hair, nails, oral mucosa and Anatomical sites of vitiligo: head and neck, trunk, upper limb, lower limb, hand and feet.
3. Washout period Prior to the investigation, all patients had not been administered any local or systemic medication for a minimum of three months.

II. Treatment protocol

The participants were divided randomly using closed envelopes into two equal groups:

- Group A: 20 patients received microneedling plus topical latanoprost solution.
- Group B: 20 patients received microneedling plus topical 5-fluorouracil 5% solution.

Steps of the procedure

The afflicted region was cleansed with betadine surgical solution, followed by a 70% alcohol solution. Prior to the surgery, a topical anaesthetic, specifically pridocaine cream, was administered on the designated location and covered with an occlusive dressing for duration of 30 minutes. The utilization of an automated microneedling device, specifically the Dr Pen Derma Pen Ultima A6®, is employed. This device is equipped with a disposable head that is tailored to the unique requirements of each patient and undergoes sterilization following each session. The derma pen was seen to penetrate the skin at depths ranging from 0.25 to 0.5 mm, which did not exceed the depth of the epidermis. The circular motion of the device was seen as it traversed the vitiligo region, resulting in the emergence of pinpoint bleeding. **(Mina et al., 2018).** Then depending on which group the patient was assigned to:

Group A: The patients were administered the LT solution, which is a pharmaceutically available eye-drop formulation with a concentration of 0.005%. The solution was promptly applied to the vitiligo patch at a rate of one drop per every 2.5 cm. Each drop included 1.5 μg of LT. **(Neinaa et al., 2021).**

Group B: The patients in the study were treated with a topical application of a 5% solution of 5-fluorouracil, which was available in ampoules under the brand name Utoral® by EIMC United Pharmaceuticals in Egypt. The solution was gently rubbed onto the afflicted area for approximately 2 minutes, and then an occlusive dressing was applied for a specified duration of time. **(Attwa et al., 2020).**

The procedures were repeated every two weeks for total duration of six months **(Mina et al., 2018)**.

III. Evaluation of the treatment

1. The lesions of all patients were captured using a digital camera prior to commencing treatment, on a monthly basis throughout the 6-month treatment course, and after the completion of the treatment.
2. Assessment of clinical repigmentation according to Physician's Global Assessment [PGA] **(Nugroho et al., 2007)**:

   G4 (excellent: >75% repigmentation)
   G3 (very good: 50%-75% repigmentation)
   G2 (good: 25%-50%)

G1 (satisfactory: <25% repigmentation)
G0 (poor: no repigmentation)

3. Vitiligo Area Scoring Index (VASI): (VASI) for each anatomical location is calculated by multiplying the area of vitiligo in hand units with the degree of depigmentation within each measured patch **(Hamzavi et al., 2004).**
4. The evaluation of the repigmentation pattern includes an assessment of its marginal, perifollicular, diffuse, and mixed characteristics.
5. Assessment of any developed side effects.

Statistical analysis

The data underwent a process of verification, coding, and analysis using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA) *. Descriptive statistics refer to the numerical measures that summarize and describe the main characteristics of a dataset. The statistical measures of means, standard deviations, medians, ranges, frequency, and percentages were computed. Statistical Significance Testing: The statistical tests employed to assess the disparity in frequency distributions among several groups were the chi-square test, Fisher's exact test, and the Monte Carlo exact test, as deemed suitable. A p-value is deemed significant if it is equal to or less than 0.05.

Results

The current study included 40 vitiligo patients, 29 females (72.5%) and 11 males (27.5%), divided into two groups. Regarding male/female ratio, it was 3/7 for FU group and 2.5/7.5 for LT group. As regarding age, both groups were matched for age (p=0.845) i.e., mean age of FU group was 24.5 ± 3.1 years and LT group was 23.7 ± 2.6 years with no significant difference.

Fourteen out of forty patients (35%) had positive family history of vitiligo and 26 patients (65%) had negative family history of vitiligo with insignificant difference between both groups.

Regarding the distribution of skin phenotype according to Fitzpatrick scales among FU group as follow: III/IV/V was 2/13/5 and in LT groups III/IV/V was 3/14/3.

Regarding disease duration it ranged from 1 to 15 years in both groups with median 2 years and mean of (3.10 ± 2.2) in 5-FU group and (3.55 ± 3.1) in LT group with insignificant difference between groups (p=0.862) **(Table. 1).**

Table 1. Socio-demographic and clinical data of the study Groups

Variables	5-FU Group (n = 20)	LT Group (n = 20)	P-value
Age (Mean ± SD)	24.45 ± 3.1	23.65 ± 2.6	= 0.845*
Sex			= 0.723**
• **Male**	6 (30%)	5 (25%)	
• **Female**	14 (70%)	15 (75%)	
Family History			= 1.000**
• **No**	13 (65%)	13 (65%)	
• **Yes**	7 (35%)	7 (35%)	
Disease Duration/years			
• **Mean ± SD**	3.10 ± 2.2	3.55 ± 3.1	= 0.862***
• **Median (Range)**	2 (1 - 9)	2 (1 - 15)	

Fitzpatrick Scale Skin Phenotype			= 0.692**
• **III**	2 (10%)	3 (15%)	
• **IV**	13 (65%)	14 (70%)	
• **V**	5 (25%)	3 (15%)	

*T-test was used to compare the mean difference between groups; **Chi-square test was used to compare the Frequency between groups; ***Mann Whitney U-test was used to compare the median between groups

Repigmentation response

There was insignificant difference (p-value = 0.317) between both treatment modalities for the degree of disease improvement. In other words, excellent/very good/satisfactory improvement was observed in 45%, 10% and 15% (n = 9, 2 and 3) in both groups. In contrast, good improvement was observed in 5% (n = 1) in FU and in 20% (n = 4) in LT group. Additionally, poor improvement was observed in 25% (n = 5) in FU and in 10% (n = 2) in LT group. The percentage of total improvement in latanoprost group reached 90% while in 5-FU group is 75% **(Fig. 1and Table .2).**

Table 2. Comparison between 5-FU group and latanoprost group according to degree of improvement

Variables	5-FU Group (n = 20)	LT Group (n = 20)	P-value
Degree of Improvement			= 0.317*
• **Excellent**	9 (45%)	9 (45%)	
• **Very Good**	2 (10%)	2 (10%)	
• **Good**	1 (5%)	4 (20%)	
• **Satisfactory**	3 (15%)	3 (15%)	
• **Poor**	5 (25%)	2 (10%)	

While 40% of both groups showed signs of marginal pigmentation, only 25% of the LT group showed signs of diffuse repigmentation, and the 5-FU group showed higher signs of perifollicular repigmentation, almost both groups showed signs of a mixed pattern of marginal and perifollicular repigmentation.

When comparing the VASI scores of both groups post-treatment to the baseline VASI, it was found that there was a significant reduction in the VASI score for both modalities (p<0.001) in which mean VASI Score at baseline (0.5± 0.1 vs 0.54 ± 0.1, p=0.730) and after treatment (0.27 ± 0.1 vs 0.26 ± 0.1, p=0.933).

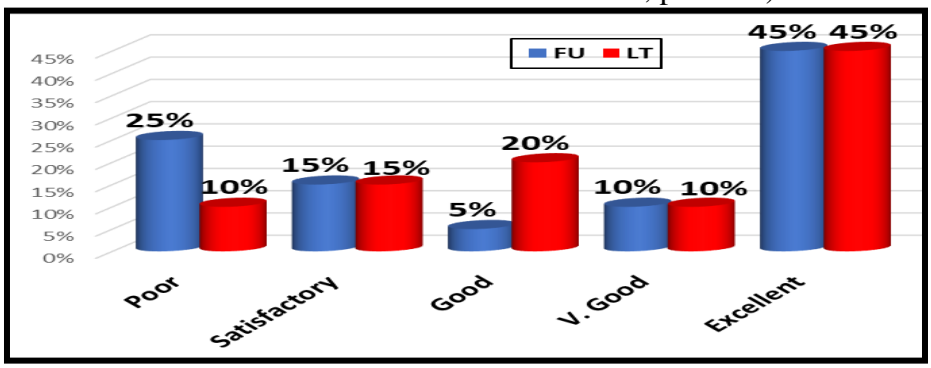

Fig. 1. Effect of Treatment on the Degree of Improvement in both groups

Relation between repigmentation and patients' demographic and clinical data

There is no relation between repigmentation and both demographic and clinical data of both groups as regarding age, sex and family history of vitiligo except for Skin Phenotype in latanoprost group where all patients with type V skin (100%) had excellent improvement (p = 0.006), followed by type IV (43%). While in 5-FU group (p = 0.107) excellent improvement was higher in type V (60%), followed by type III (50%). Also, it was noted absence of poor responders among patients with type V skin in both groups.

There was statistically significant difference between the different improvement degrees regarding the mean disease duration in years (p = 0.049). Patients with excellent/very good improvement had significantly shorter DD (2.4 ± 0.5 years) compared to those with good/satisfactory improvement and poor outcome **(Fig.2).**

Fig.2. Relation of Disease Duration and Improvement Degree

Relationship between Improvement Degree and Lesion Site

With regard to different body sites, 5-FU showed excellent to good improvement in different body sites specially legs and knees 63% (n = 7) **(Fig.3& Fig.5),** arms 45.5% (n = 5), trunk 25% (n = 1) and one case of foot lesions (25%) showed good improvement. While in latanoprost group excellent to good improvement was mostly noted in face 45.5% (n = 6) **(Fig. 4& Fig.6)** and 28.6% (n = 2) respectively followed by foot lesions 36.4% (n = 4) show excellent improvement and 42.9% (n = 3) show good improvement then arms, elbows and trunk **(Table .3).**

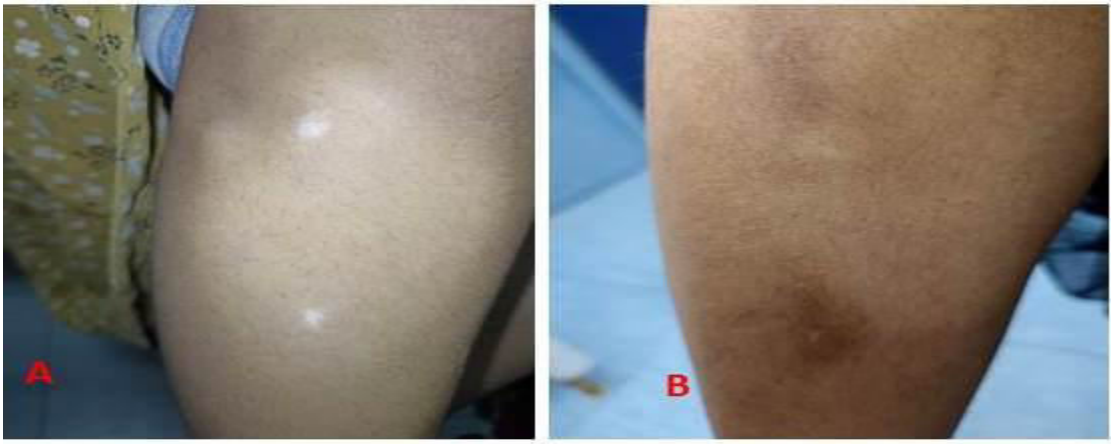

Fig. 3. Lower limb of 18 years old female patient from group B: (a) before treatment, (b) after 6 months treatment with microneedling with 5 FU showing G4 repigmentation.

Fig.4. Face of 18 years old female patient from group A: (a) before treatment. (b) after 6 months of treatment of microneedling with latanoprost showing G4 repigmentation.

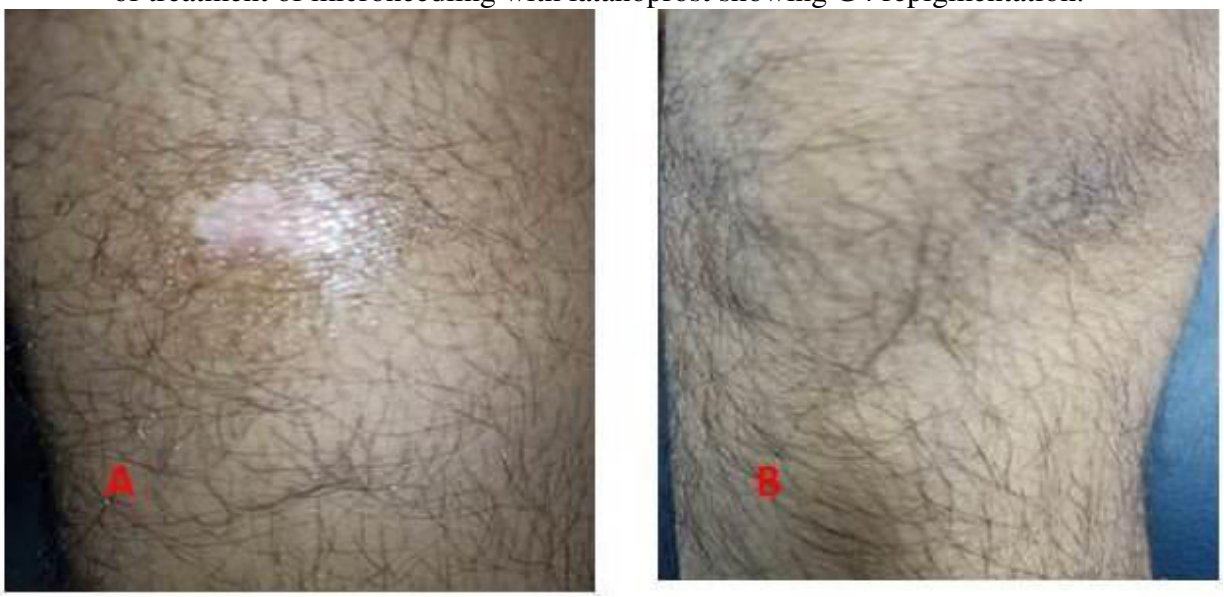

Fig.5. Lower limb of 25 years old male patient from group B: (a) before treatment, (b) after 6 months treatment with microneedling with 5 FU showing G4 repigmentation.

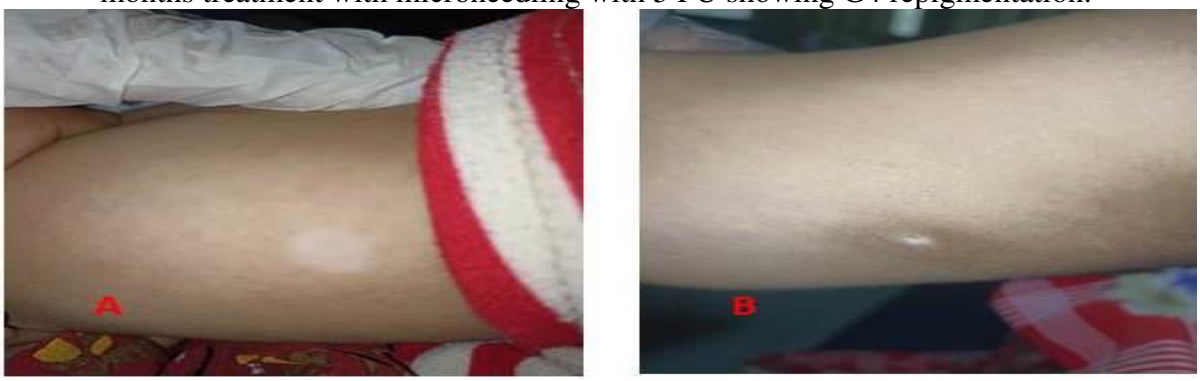

Fig. 6. Upper limb of 14 years old female patient from group A: (a) before treatment. (b) after 6 months of treatment of microneedling with latanoprost showing G4 repigmentation

Table 3. Relationship between Improvement Degree and Lesion Site (Total Sample)

Variables	Improvement Degree			P-value*
	Excellent/V. Good (n = 22)	Good/Satisfactory (n = 11)	Poor (n=7)	
Site of Lesion				
• **Elbow**	0 (0%)	2 (18.2%)	0 (0%)	= 0.098
• **Arm**	7 (31.8%)	0 (0%)	1 (14.3%)	**= 0.034**
• **Foot**	4 (18.2%)	4 (36.4%)	4 (57.1%)	**= 0.036**
• **Leg**	7 (31.8%)	4 (36.4%)	1 (14.3%)	**= 0.048**
• **Face**	6 (27.3%)	0 (0%)	1 (14.3%)	= 0.149
• **Neck**	1 (4.5%)	1 (9.1%)	1 (14.3%)	= 0.297
• **Trunk**	0 (0%)	2 (18.2%)	0 (0%)	= 0.098

*Monte Carlo exact test was used to compare the Frequency between groups

Side effects

Ninety five percent of the patients reported burning sensation and pain during the procedure but was well tolerated, there was only one patient in 5-FU group (5%) developed hyperpigmentation with no systemic side effects at all, while in latanoprost group there were no reported complications.

Discussion

Due to the fact that vitiligo can be a significant cosmetic problem for patients, a number of methods are currently available to help fight for a better skin appearance **(Frączek et al., 2022)**. None of the different therapeutic methods proposed so far for managing vitiligo has been significantly effective **(Kundu et al., 2019)**. Stable vitiligo can be treated with a wide range of techniques, each of which has a different effect depending on the clinical features of the affected area, the severity of the lesions, the presence of additional autoimmune disease and the techniques employed**,** still studies are needed to reach ideal treatment **(Kumar et al., 2019; Ziaeifar et al., 2021)**.

In the current study we tried to compare the clinical efficacy of topical 5-fluorouracil after skin microneedling versus topical latanoprost after skin microneedling in the induction of skin repigmentation in localized stable vitiligo patients. We found that both modalities of treatment showed variable degree of repigmentation of vitiligo lesions with insignificant difference.

Till now, no previous study compared latanoprost and 5-flourouracil after microneedling.

These results were very close to a previous study of 25 patients with localized stable nonsegmental vitiligo, compared microneedling plus 5-fluorouracil 5% with microneedling versus tacrolimus of two patches in the same patient every two weeks for six months and found the excellent result was 48% and 4% very good response with 5-FU group and a statistically significant difference between both arms of the study **(Mina et al., 2018)**. In contrast, the current study examined 20 patients independently in each group, finding that there was no statistically significant difference between the two groups and that up to 55% of patients had excellent or very good responses. Also, the prior study employed 5-FU solution in liposomal basis daily between the sessions, in contrast 5-FU% solution was only used at the time of the microneedling sessions which may suggest that there is indifference between both modalities.

Another study conducted on fifty patient with stable yet resistant vitiligo and subjected to microneedling followed by 5-FU application every two weeks for 3 months, resulted in 60% total response of repigmentation in the lesions, complete pigmentation in very small patches and 40% did not have any response **(Santosh et al., 2018)**. In contrast to our study showed 60% excellent, very good and good response, 15% satisfactory and only 25% poor response to 5-FU. This may be explained by those patients in their study had treatment duration of only 3 months, also patients selected for the previous study showed no response for conventional therapies for 2-3 years before their study. In the current work both naïve and previously non responders were concluded.

(Attwa et al., 2020) also investigated the additional effect of needling and 5-FU to needling alone in 27 localized vitiligo patients for 3 months, reported a better response in the combination of needling and topical 5-FU, yet the results of improvement were 3.7% excellent response and 3.7% very good response. Small sample size and short duration of the latter study compared to the current study, gave our study a better result.

In contrast to the current study, **(Sethi et al., 2007)** who studied the combination of dermabrasion and 5-FU 5% cream on 30 patches of stable vitiligo and found that the efficacy of dermabrasion combined with 5-fluorouracil was 56.67% at 4 months and 73.33% at 6 months. These higher results explained by the use of 5-FU cream instead of solution in the current study and the use of dermabrasion which facilitate a deeper absorption. Although the same reasons of the higher response led to Multiple side effects observed in the previous study as Delayed healing up to 3-4 weeks from deep wounds, pseudomembranous formation and hypertrophic scarring and hyperpigmentation which was not detected with microneedling advantages of rapid healing without scarring in our study**.**

On the other hand, **(Anbar et al., 2015)** investigated the effect of latanoprost as a monotherapy in vitiligo and found a 43% excellent to good responses out of 14 patients. In the current work the enhanced effect of microneedling in combination with topical latanoprost gave better results up to 55% excellent to very good responses.

A recent study conducted to evaluate the efficacy of NBUVB, microneedling and topical latanoprost combination for 6 months. The study revealed repigmentation improvement >50% in 48% of 50 patients **(Neinaa et al., 2021).** In contrast to the current study with superior results on latanoprost group and repigmentation response >50% in 55% of 40 patients. The better results in the current study may be explained by the synergistic effect of microneedling to induce the repigmentation and possibly equal and controlled distribution of topical latanoprost in the dermis.

As regard the type of repigmentation, **(Attwa et al., 2020)** agreed with the current study and found a perifollicular and marginal repigmentation patterns were noted after treatment with microneedling and 5-FU. **(Neinaa et al., 2021)** also agreed that perifollicular and diffuse repigmentation are most prominent after microneedling with latanoprost.

When comparing the VASI scores of both groups post-treatment to the baseline, it was found that there was a significant reduction in the VASI scores due to the influence of both modalities in this study.

Consistent with the present investigation, a previous study assessed the clinical impact of topical 5-FU and microneedling on VASI scores for a period of three months, observing a noteworthy decrease in VASI

score mean (3.5 ± 2.8) and median (2.6) values post-treatment relative to pre-treatment values (mean of 4.4 ± 2.7 and a median of 4.1) (Wilcoxon = 4.5, $p < 0.001$). Our study generated a 45% great response, compared to 40% excellent response in the previous trial, meaning that when comparing the entire clinical response, our results were superior. **(Abdou et al., 2022).**

In our study there was statistically significant difference between the different improvement degrees regarding the mean disease duration in years ($p = 0.049$). This finding was in agreement with previous studies done by **(Neinaa et al., 2021)** and **(Anbar et al., 2015)**. Another author concluded a negative correlation between disease duration and amount of pigment production after treatment **(Nowroozpoor Dailami et al., 2020).** This is explained by the exhaustion of follicular outer rout sheath melanocytes in longstanding cases **(Anbar et al., 2009)**.

With regard to different body sites, 5-FU showed excellent to good improvement in different body sites specially legs, knees, arms, trunk and one case of foot lesions showed good improvement. While in latanoprost group excellent to good improvement was mostly noted in face followed by foot lesions, arms, elbows and trunk.

This agreed with **(Mina et al., 2018)** and other studies on 5-FU listed that truncal and extremities lesions were the best responders to 5-FU while acral lesions showed the least improvement **(Abd El-Samad & Shaaban, 2012):(Shashikiran et al., 2018)**. While in latanoprost group excellent to good improvement was mostly noted in face followed by foot lesions, arms, elbows and trunk also in agreement with and **(Neinaa et al., 2021)**.

It was noted in the current study results a significant difference in face lesions distribution as FU group had significantly lower percentage of face affection (0%) compared with LT group (35%). This follows **(Shashikiran et al., 2018)** and **(Mina et al., 2018)** who excluded face lesions when treating vitiligo with 5-FU. According to **(Anbar et al., 2015)** and **(Eldelee et al., 2021)** face lesions have the best repigmentation response compared to other body parts. According to **(Halder & Chappell, 2009)**, facial skin has greater permeability, more residual melanocytes in the unaffected skin, more follicular reservoirs, so melanocyte injury can be restored more easily.

Regarding the side effects, our study agreed with **(Korobko & Lomonosov, 2016)** and **(Neinaa et al., 2021)** who reported minimal or absence of any side effects with latanoprost use in treatment of vitiligo. On the 5-FU side **(Attwa et al., 2020)** and **(Mina et al., 2018)** both also reported a minimal side effects with 5-FU use of transient pain and itching, with reported 16% hyperpigmentation reported as a side effect with Mina et al, and absence of systemic complication **(Mina et al., 2018)**.

Conclusion

The combination of microneedling with either 5-Flourouracil or latanoprost is safe and effective in treatment of localized stable vitiligo. Although, the total response in latanoprost group was higher, it did not reach statistical significance. However further studies of combining different therapies as phototherapy or radiofrequency microneedling to increase the efficacy of the treatment and to follow up any possible long term side effects.

Compliance of Ethics Guidelines

The present study received ethical approval from the Ethics Committees at the Faculty of Medicine, South Valley University, under approval number 370/3/22. The study was carried out in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Institutional

Review Board-Ethics committee of the Faculty of Medicine at South Valley University.

Patients Consent

A written consent was obtained and signed by every subject in the study for agreement to publish study data, including photos and other materials.

Consent for publication

The researchers acquired written informed consent from the subject for the purpose of publication.

Conflict of interest statement: The authors assert that they have no conflicts of interest.

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References

- **Abd El-Samad Z, Shaaban D. (2012).** Treatment of localized non-segmental vitiligo with intradermal 5-flurouracil injection combined with narrow-band ultraviolet B: a preliminary study. J Dermatolog Treat, 23(6): 443-448.
- **Abdou AG, Farag AGA, Rashwan M, Shehata WA. (2022).** The clinical and pathological effectiveness of microneedling and topical 5-fluorouracil in vitiligo treatment: An association with matrix metalloproteinase 2 immunohistochemical expression. Journal of Cosmetic Dermatology, 21(5): 2153-2161.
- **Anbar TS, Abdel-Raouf H, Awad SS, Ragaie MH, Abdel-Rahman AT. (2009).** The hair follicle melanocytes in vitiligo in relation to disease duration. J Eur Acad Dermatol Venereol, 23(8): 934-939.
- **Anbar TS, El-Ammawi TS, Abdel-Rahman AT, Hanna MR. (2015).** The effect of latanoprost on vitiligo: a preliminary comparative study. Int J Dermatol, 54(5): 587-593.
- **Attwa EM, Khashaba SA, Ezzat NA. (2020).** Evaluation of the additional effect of topical 5-fluorouracil to needling in the treatment of localized vitiligo. Journal of Cosmetic Dermatology, 19(6): 1473-1478.
- **Bae JM, Jung HM, Hong BY, et al. (2017).** Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. JAMA Dermatol, 153(7): 666-674.
- **Bergqvist C, Ezzedine K. (2020).** Vitiligo: A Review. Dermatology, 236(6): 571-592.
- **Eldelee SA, Gheida SF, Sarhan NI, Ibrahim ZA, Elfar NN. (2021).** Evaluation of the effect of combined intralesional injection of prostaglandin F2α with narrow band UVB phototherapy in treatment of resistant cases of vitiligo. Journal of Dermatological Treatment, 32(4): 383-390.
- **Frączek A, Kasprowicz-Furmańczyk M, Placek W, Owczarczyk-Saczonek A. (2022).** Surgical Treatment of Vitiligo. Int J Environ Res Public Health, 19(8):4812.
- **Gauthier Y, Anbar T, Lepreux S, Cario-André M, Benzekri L. (2013).** Possible mechanisms by which topical 5-Fluorouracil and dermabrasion could induce pigment spread in vitiligo skin: an experimental study. ISRN Dermatol, 2013: 852497.
- **Halder RM, Chappell JL. (2009).** Vitiligo update. Semin Cutan Med Surg, 28(2): 86-92.
- **Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. (2004).** Parametric modeling of narrowband UV-

B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. Arch Dermatol, 140(6): 677-683.

- **Korobko IV, Lomonosov KM. (2016).** A pilot comparative study of topical latanoprost and tacrolimus in combination with narrow-band ultraviolet B phototherapy and microneedling for the treatment of nonsegmental vitiligo. Dermatol Ther, 29(6): 437-441.
- **Kumar A, Bharti R, Agarwal S. (2019).** Microneedling with Dermaroller 192 needles along with 5-fluorouracil solution in the treatment of stable vitiligo. J Am Acad Dermatol, 81(3): e67-e69.
- **Kundu RV, Mhlaba JM, Rangel SM, Le Poole IC. (2019).** The convergence theory for vitiligo: A reappraisal. Exp Dermatol, 28(6): 647-655.
- **Mina M, Elgarhy L, Al-Saeid H, Ibrahim Z. (2018).** Comparison between the efficacy of microneedling combined with 5-fluorouracil vs microneedling with tacrolimus in the treatment of vitiligo. J Cosmet Dermatol, 17(5): 744-751.
- **Neinaa YME, Lotfy SS, Ghaly NR, Doghaim NN. (2021**). A comparative study of combined microneedling and narrowband ultraviolet B phototherapy versus their combination with topical latanoprost in the treatment of vitiligo. Dermatol Ther, 34(2): e14813.
- **Nowroozpoor Dailami K, Hosseini A, Rahmatpour Rokni G, et al. (2020).** Efficacy of topical latanoprost in the treatment of eyelid vitiligo: A randomized, double-blind clinical trial study. Dermatologic Therapy, 33(1): e13175.
- **Nugroho H, Fadzil MH, Yap VV, Norashikin S, Suraiya HH. (2007).** Determination of skin repigmentation progression. Annu Int Conf IEEE Eng Med Biol Soc, 2007: 3442-3445.
- **Salloum A, Bazzi N, Maalouf D, Habre M. (2020).** Microneedling in vitiligo: A systematic review. Dermatol Ther, 33(6): e14297.
- **Santosh S, Sushantika ML, Gupta A, Mohammad A, Kumar N. (2018).** Treatment of vitiligo with 5-fluorouracil after microneedling of the lesion. Int J Sci Stud, 5(11): 125-127.
- **Sethi S, Mahajan BB, Gupta RR, Ohri A. (2007).** Comparative evaluation of the therapeutic efficacy of dermabrasion, dermabrasion combined with topical 5% 5-fluorouracil cream, and dermabrasion combined with topical placentrex gel in localized stable vitiligo. Int J Dermatol, 46(8): 875-879.
- **Shashikiran AR, Gandhi S, Murugesh SB, Kusagur M. (2018**). Efficacy of topical 5% fluorouracil needling in vitiligo. Indian J Dermatol Venereol Leprol, 84(2): 203-205.
- **Tsuji T, Hamada T. (1983).** Topically administered fluorouracil in vitiligo. Arch Dermatol, 119(9): 722-727.
- **Ziaeifar E, Ziaeifar F, Mozafarpoor S, Goodarzi A. (2021).** Applications of microneedling for various dermatologic indications with a special focus on pigmentary disorders: A comprehensive review study. Dermatologic Therapy, 34(6): e15159.