Al-Azhar International Medical Journal

Volume 5 | Issue 4 Article 32

4-30-2024
Section: Dermatology

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How to Cite This Article

Abdel Aal, Essam Bakr; Fahmy, Sameh Fawzy; and Kandil, Hassan Abdalla Hassan (2024) "Fractional CO2 laser versus Microneedling followed by Topical 5 Fluorouracil in the treatment of Non-Segmental Vitiligo," *Al-Azhar International Medical Journal*: Vol. 5: Iss. 4, Article 32.
DOI: https://doi.org/10.58675/2682-339X.2376

ORIGINAL ARTICLE

Fractional CO_2 laser versus Microneedling followed by Topical 5 Fluorouracil in the treatment of Non-Segmental Vitiligo

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Abstract

Background: ***Milky white macules and patches on the skin and mucous membrane are characteristic of vitiligo, an acquired idiopathic progressive depigmenting illness marked by a significant loss of functional epidermal and, in some cases, hair follicle melanocytes.***

Objective: This research aims to evaluate the efficiency of treating vitiligo with microneedling with a fractional CO2(FrCO2) laser followed by topical 5 Fluorouracil (5-FU).

Subjective: ***The research is a comparative clinical research performed at the Dermatology outpatient clinic of Al-Azhar University Hospitals on thirty (30) patients diagnosed clinically as vitiligo in which they were split into two groups at random, Group I: Application FrCO2laser followed by topical 5-FU and Group II: Application of microneedling followed by 5-FU.***

Results: ***Patients undergoing systemic cancer treatment frequently use 5-FU. It forms the backbone of several different types of combination chemotherapy. The use of 5-FU to treat cancer has been linked to the development of localized hyperpigmentations.***

Conclusion: ***In treating vitiligo, employing a combination of FrCO2 laser or microneedling with 5-FU rather than utilizing either is a more effective and safe technique. Patients who undergo this process will benefit from a new therapeutic window.***

Keywords: Fractional CO2 laser; Microneedling; Non Segmental Vitiligo; Topical 5 Fluorouracil

1. Introduction

The loss of melanocytes (pigment cells) from the epidermis and other tissues is the defining feature of vitiligo, a common pigmentary skin condition. Only 0.5-1% of the population is impacted. Various medicinal treatments, such as topical and systemic corticosteroids, topical calcineurin inhibitors, and phototherapy, are available for vitiligo.[1]

However, therapies do not pigment all lesions and only rarely lead to total repigmentation of the affected lesions.[2]

Transdermal drug delivery via microneedling improves the efficacy of topical immunomodulator medications. Since a microneedling device is applied to the skin, micropores or transport channels through the stratum corneum are formed. Drug absorption, effectiveness, and treatment duration can all be enhanced through this method.

Moreover, microneedling allows the epidermis to remain largely intact, accelerates the healing process, and reduces the likelihood of infection and scarring.[3]

In combination with NB-UVB, topical 5-FU was administered to treat vitiligo, but dermabrasion was performed first.[4]

Accepted 14 April 2024.
Available online 30 April 2024

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https://doi.org/10.58675/2682-339X.2376

Although 5-FU has been known to have an antimitotic impact, its topical application has only recently been linked to increased melanocyte proliferation and migration. Direct overstimulation of melanocyte proliferation, inhibition of agents or cells able to destroy pigment cells, and finally, immunomodulation stabilizing the vitiligo have all been hypothesized to stimulate the reservoir of follicular melanocytes or the persistent Dopa-negative melanocytes in the depigmented epidermis.[5]

Individuals undergoing systemic cancer treatment frequently use 5-fluorouracil (5-FU). It forms the backbone of several different types of combination chemotherapy.[6]

Localized hyperpigmentations have been reported as a side effect of 5-FU for the treatment of cancer.[7]

The aim is to compare the efficacy of treating vitiligo with microneedling and FrCO2laser, followed by applying 5-FU.

2. Patients and methods

The research is a comparative clinical study performed at the Dermatology outpatient clinic of Al-Azhar University Hospitals on thirty (30) patients diagnosed clinically with vitiligo. The patients were randomly separated into Group I, which applied FrCO2 laser followed by topical 5-FU, and Group II, which applied microneedling followed by 5-FU.

The study lasted one year, from January 2022 to January 2023. All individuals gave written consent before participating in the study after being informed of its objectives and procedures. The approval came from the research ethical committee and the Institutional Review Board (IRB) of the Faculty of Medicine, Al-Azhar University. All human subjects research shall be conducted in a manner consistent with the Declaration of Helsinki, a code of ethics established by the World Medical Association.

Inclusion criteria: Healthy adult patient with a clinical diagnosis of vitiligo.

Exclusion criteria: Hypersensitivity, poor nutritional status, myelosuppression, severe infections, and recent surgery.

Operational design

The participants underwent a complete history taking, including personal, complaint, present, past, and family history, and a full clinical examination, either general for all systems or local dermatological examination.

Application of FrCO2 laser followed by topical 5-FU to the group I

After deciding which vitiligo patches needed to be treated, a local anesthetic cream (Lidocaine 25% and Prilocaine 25%) was applied to all vitiligo lesions 30 minutes before the procedure. Then, the lesions were cleaned with 70% alcohol. After treating the patches with a FrCO2laser (DEKA, SmartXide DOT), a 5% solution (50 mg/ml) of 5-fluorouracil was dropped with an insulin syringe (28G × ½) and rubbed into the treated area until it disappeared (FrCO2 + 5-FU).8

The vitiligo lesion was thoroughly medicated with FrCO2, which involves the area beyond the patch's edge. Bleeding points were considered the terminus of FrCO2. Treatment parameters included 14 Watts, 550-m spacing, 400-µs dwell time, scanning mode, and a single stack. Patients attended three sessions spaced out every two weeks. Patients were advised to limit their time in the sun and to protect any exposed skin with an SPF 50 broad-spectrum sunscreen.[8]

Application of micro-needling followed by 5-FU to group II

Microneedling is based on the principles of neovascularization and neocollagenesis, which occur in response to microinjuries caused by needle penetration. Until bleeding appeared, an electronic derma pen with needle thickness varying from 1 or 1.5 to 2 mm based on the thickness of the epidermis was utilized. The patient received six to twelve sessions every two weeks. Following microneedling, a 5% (5 mg/ml) solution of 5-FU was administered topically to the affected areas and covered with an occlusive dressing for one day. The patient was instructed to administer 5-FU once per day for fourteen days.[9]

Digital photographs were taken at baseline weekly before each session and after treatment and follow-up.

Statistical Analysis

SPSS, version 22 software (SPSS Inc., Chicago, Illinois, USA) was used to analyze the data collected for this investigation. Quantitative study variables were summarized as means ± standard deviation. Percentages were used to display the qualitative variables. The x2 test and Fisher's exact test were used to compare the outcomes of the two groups, with the latter being used for the study of smaller samples only.

Independent T-test for comparing parametric means between two groups, and Mann-Whitney test for comparing non-parametric quantitative variables. Paired T-test was used to compare two means in the same group before and after the procedures. Pearson's correlation assessed the association between two parametric quantitative variables. The FF-test, or Analysis of variance (ANOVA), was used to compare means between three groups. Linear regression was used to predict factors associated with PGA scores. P values below 0.05 were considered significant.

3. Results

Table 1. Characteristics of the examined groups.

Variable		*Group I (n=15)*		*Group II (n=15)*		*Total*		*Test*	*P*
Age: (days)	*Mean ± SD*	24.07 ±		28.07 ±		26.07 ±		MW	
	Median	7.88		8.39		8.25		test =	0.233
	Range	22.00		30.00		22.00		83.00	NS
		18.00-45.00		18.00-45.00		18.00-45.00			
Variable		**No**	**%**	**No**	**%**	**No**	**%**	χ^2	**P**
Gender:	Female	8	53.3%	10	66.7%	18	60%	0.556	0.456
	Male	7	46.7%	5	33.3%	12	40%		NS
Family history	Positive	7	46.7%	6	40%	13	43.3%	0.136	0.713
	Negative	8	53.3%	9	60%	17	56.7%		NS
Other autoimmune	Positive	3	20%	3	20%	6	20%	FEX=	1.00
	Negative	12	80%	12	80%	24	80%	0.00	NS
Fitzpatrick Skin type	type II	3	20%	7	46.7%	10	33.3%	FEX=	0.289
	type III	9	60%	5	33.3%	14	46.7%	2.714	NS
	type IV	3	20%	3	20%	6	20%		
Type of vitiligo	Generalized	7	46.7%	5	33.3%	12	40%	0.556	0.456
	Localized	8	53.3%	10	66.7%	18	60%		NS
Duration of vitiligo	Mean ± SD	3.73 ± 1.91		4.93 ± 1.94		4.33 ± 1.99		T	
	Median	4.00		5.00		4.00		test=	0.099
	Range	1.00-8.00		2.00-9.00		1.00-9.00		1.706	NS

SD: standard deviation, T test: Independent T test, MW: Mann Whitney test, FEX: Fisher Exact Test,
NS: non-significant >0.05

Table 1 shows that 30 patients, comprising 18 women and twelve men, with stable vitiligo, with a mean age 26.07 ± 8.25 years and range of 18-45 years, were included in this comparative study dividing patients in two groups applying two techniques of treatment (fractional laser followed by FU and microneedle followed by FU), fifteen patients in each group. The mean duration of vitiligo was 4.33 ± 1.99 years, with range of 1-9 years.

Regarding the distribution of demographics and medical history between groups. There was no significant variation concerning gender, age, other autoimmune, family history, type of vitiligo, Fitzpatrick Skin type and duration of disease.

Table 2. Distribution of sites of patches of the examined groups.

SITE OF PATCHES	GROUP I (*N*=15)		GROUP II (*N*=15)		TEST	P
	No	%	No	%		
TRUNK	6	40%	5	33.3%	FEX=	0.441
FACE	2	13.3%	3	20%	5.550	NS
FEET	2	13.3%	0	0%		
HAND	2	13.3%	0	0%		
EXTREMITIES	2	13.3%	3	20%		
HAND AND FEET	1	6.8%	4	26.7%		

FEX: Fisher Exact Test

Table 2 shows distribution of sites of patches of vitiligo in the studied groups, there was no significant distinction among both groups (p=0.441), the most affected site was trunk in both groups, (40% in fractional group versus 33.33% in microneedle group) and the least affected site was hand and feet in both groups (13.33% fractional group versus 0% in microneedle group).

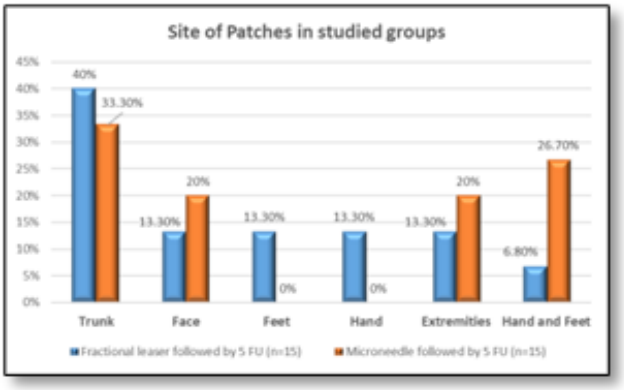

Figure 1. Distribution of site of patches of vitiligo in studied groups.

Table 3. Physician Global Assessment (PGA) Score at the beginning before application of both procedures of the studied groups.

SCORING		GROUP I (*N*=15)		GROUP II (*N*=15)		TEST	P
		No	%	No	%		
EXCELLENT (>75%)		0	0%	0	0%	FEX= 1.285	0.706 NS
GOOD (50–75%)		1	6.7%	0	0%		
MODERATE (25–50%)		6	40%	5	33.3%		
POOR (<25%)		8	53.3%	10	66.7%		
SCORING PERCENTAGE	*Mean ± SD*	32.33% ± 19.35%		27.0% ± 18.11%		T test = 0.779	0.442 NS
	Median	25.0%		25.00%			
	Range	00.0%-60.00%		0.00%-50.00%			

Table 3 shows the distribution of the (PGA) score intervals before application of both procedures in the examined groups, there was no significant disparity in PGA score amongst groups, (32.33% ± 19.35% versus 27.0% ± 18.11%, p=0.442). Most of patients in both groups showed poor status (53.33% and 66.7%, correspondingly), with no significant variation among both groups (p=0.706).

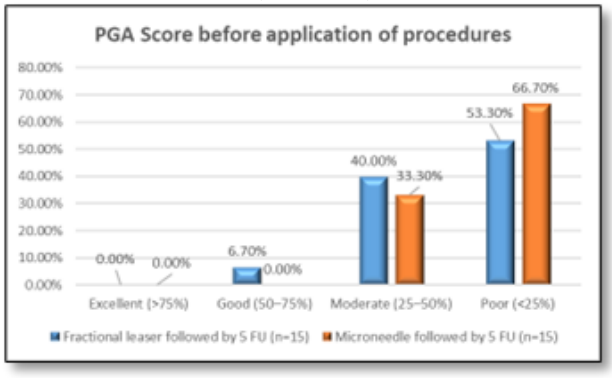

Figure 2. PGA score before application of procedures in examined groups.

Table 4. PGA score of improving after both procedures of the groups.

SCORING		GROUP I (*N*=15)		GROUP II (*N*=15)		TEST	P
		No	%	No	%		
EXCELLENT (>75%)		5	33.3%	1	6.7%	FEX= 6.861	0.071 NS
GOOD (50–75%)		5	33.3%	2	13.3%		
MODERATE (25–50%)		3	20%	5	33.3%		
POOR (<25%)		2	13.4%	7	46.7%		
SCORING PERCENTAGE	*Mean ± SD*	59.33% ± 26.72%		38.67% ± 22.56%		T test = 2.289	0.030* S
	Median	60.0%		40.00%			
	Range	00.0%-90.00%		0.00%-80.00%			

Table 4 shows the distribution of improving of the PGA score intervals after both procedures in the investigated groups, there was significant increase in PGA score in group I in contrast to group II, (59.33% ± 26.72% versus 38.67% ± 22.56%, p=0.030*). Most of patients in group I showed excellent and good improvement (33.3% for both), compared to poor and moderate improvement in group II (46.7% and 33.3%, correspondingly), with non- significant distinction among both groups (p=0.071).

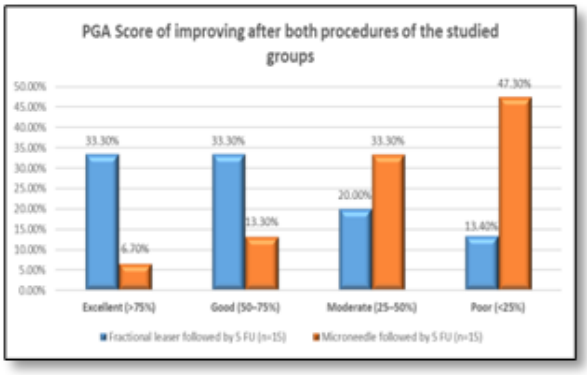

Figure 3. Distribution of PGA score in studied groups.

Table 5. Comparison between PGA score before and after procedures in studied groups.

VARIABLE		GROUP I (*N*=15)	GROUP II (*N*=15)	TOTAL (N=30)	INDEPENDENT T TEST	P
SCORING PERCENTAGE BEFORE	*Mean ± SD*	32.33% ± 19.35%	27.0% ± 18.11%	29.67% ± 18.61%	T test=0.779	0.442 NS
	Median	25.0%	25.00%	25.00%		
	Range	00.0%-60.00%	0.00%-50.00%	0.00%-60.00%		
SCORING PERCENTAGE AFTER	*Mean ± SD*	59.33% ± 26.72%	38.67% ± 22.56%	49.00% ± 26.47%	T test=2.289	0.030* S
	Median	60.0%	40.00%	50.00%		
	Range	00.0%-90.00%	0.00%-80.00%	0.00%-90.00%		
TEST OF SIGNIFICANCE (PAIRED T TEST)		T=10.136	T=4.249	T=8.200		
P VALUE		0.000* S	0.001* S	0.000* S		

Table 5 shows that there was highly significant increase in PGA scores after procedures compared to before application in group I (32.33% ± 19.35% versus 59.33% ± 26.72%, p=0.000) and in group II (27.0% ± 18.11% versus 38.67% ± 22.56%, p=0.000).

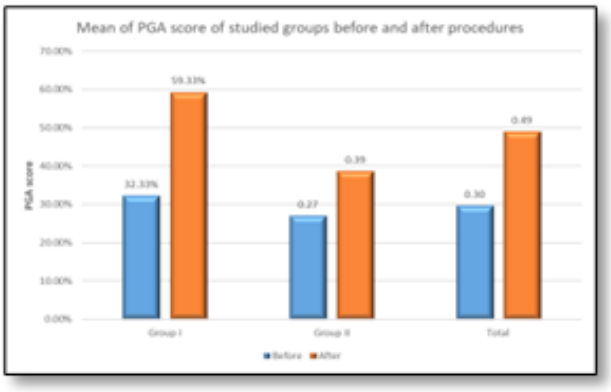

Figure 4. The PGA score in studied groups before and after procedures.

Table 6. Effect of different factors on PGA Score of improving after Fractional leaser followed by 5 FU in group 1 (n=15).

SCORING PERCENTAGE	GENDER				
	Male	Female		TEST	P
MEAN ± SD	60.71%±25.40%	58.13%±29.51%		T test= 0.181	0.859 NS
	Family History				
	Positive	Negative			
MEAN ± SD	37.14%±21.96%	78.75%±9.54%		T test=4.644	0.002* S
	Other Autoimmune				
	Positive	Negative			
MEAN ± SD	21.67%±20.21%	68.75%±18.72%		T test=3.847	0.002* S
	Fitzpatrick Skin type			Test	P
	Type II	Type III	Type IV		
MEAN ± SD	68.33% ±16.07%	56.11%±32.29%	60.00%±20.00%	F test= 0.210	0.814 NS
	Type of Vitiligo				
	Generalized	Localized			
MEAN ± SD	52.86%±30.38%	65.00%±20.87%		T test=0.871	0.400 NS

F test: ANOVA analysis, S: significant<0.05

Table 6 shows the distribution of PGA score after fractional laser followed by FU according to variant factors. There was no significant difference in scores regarding gender, Fitzpatrick Skin type and type of vitiligo. While, there was significant increased score in negative family history and negative other autoimmune compared to patients with positive history and other autoimmune diseases, (p=0.002 for both).

Table 7. Effect of different factors on PGA score of improving after Microneedle followed by 5 FU in group 2 (n=15).

SCORING PERCENTAGE	GENDER			
	Male	Female	TEST	P
MEAN ± SD	34.00%±20.43%	41.00%±24.24%	T test=0.552	0.590 NS
	Family History			
	Positive	Negative		
MEAN ± SD	25.00%±18.44%	47.78%±21.08%	T test=2.193	0.047* S
	Other Autoimmune			
	Positive	Negative		
MEAN ± SD	16.67%±20.82%	44.17%±20.09%	T test=2.108	0.029* S
	Fitzpatrick Skin type			Test P
	Type II	Type III	Type IV	
MEAN ± SD	35.71% ±24.40%	40.00%±28.94%	33.33% ±14.34%	F test=0.012 0.988 NS
	Type of Vitiligo			
	Generalized	Localized		
MEAN ± SD	22.00%±18.91%	47.00%±20.03%	T test=2.318	0.037* S

F test: ANOVA analysis, S: significant<0.05

Table 7 shows the distribution of PGA score after microneedle followed by FU according to variant factors. There was no significant difference in scores regarding gender, Fitzpatrick Skin type and type of vitiligo. While there was significant increased score in negative family history and negative other autoimmune compared to patients with positive history and other autoimmune diseases, (p=0.047 and 0.029).

Table 8. Correlation between PGA score and age and disease duration in both groups.

VARIABLE	PGA SCORE			
	Group 1		Group 2	
	R	P	R	P
AGE	- 0.419	0.048* S	- 0.824	0.000* S
DISEASE DURATION	- 0.516	0.039* S	- 0.621	0.013* S

R: Pearson`s correlation coefficient, S: significant <0.05

Table 8 shows that there was negative moderate correlation among PGA score, age and vitiligo duration in group I and there was strong negative correlation between PGA score, age and vitiligo duration in group II.

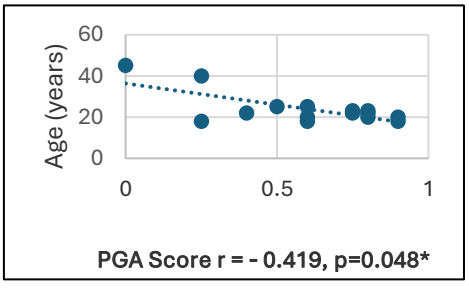

Figure 5. Correlation between PGA and age in group I.

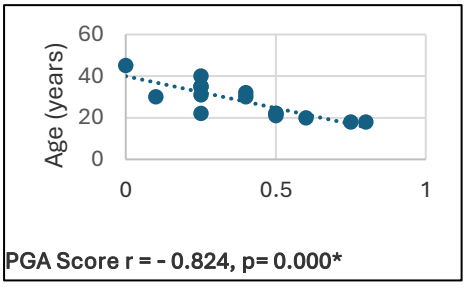

Figure 6. Correlation between PGA and age in group II.

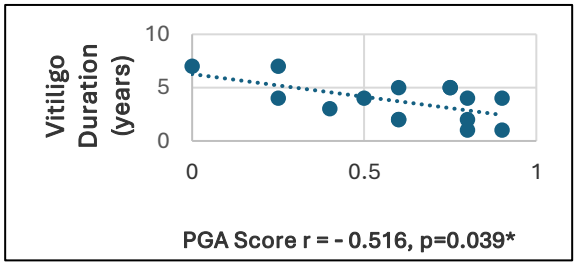

Figure 7. Correlation between PGA and vitiligo duration in group I.

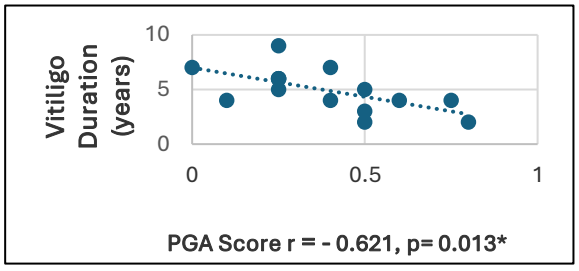

Figure 8: Correlation between PGA and vitiligo duration in group II.

4. Discussion

The FrCO2laser has been proven to treat vitiligo lesions alone or in combination with sun exposure, narrowband UVB phototherapy, or topical five fluorouracil (5-FU). Its application as a way of delivering 5-FU. Furthermore, FrCO2 laser increases the synthesis of several cytokines, such as transforming growth factor 1, which is reduced in some vitiligo patients.[10]

Marchioro et al. hypothesized that The reservoir of follicular melanocytes or the persistent Dopa-negative melanocytes in the depigmented epidermis might be stimulated through direct overstimulation of melanocyte proliferation, inhibition of agents or cells that can destroy pigment cells, and finally, immunomodulation that stabilizes Vitiligo.[11]

Regarding the distribution of demographics and medical history between groups, there was no significant distinction concerning age, family history, gender, other autoimmune, Fitzpatrick skin type, type of Vitiligo, and duration or site of disease.

The research of Weshahy et al. was performed on 30 vitiligo cases. Their ages varied from 18 to 63 years with mean ± SD (36.3 ± 14.1), with a male: female ratio of 1:1. No statistically significant correlation was found between their participants regarding age, sex, the degree of repigmentation, the skin phototype, or the duration of the disease.[12]

Also, the findings of similar studies by Makki, Kim et al. came to be in the same line with our results as they showed that there was no association among their studied patients considering age, gender, family history, skin type, type of Vitiligo and duration or site of disease.[13,14]

Regarding the distribution of the PGA score intervals before the application of both procedures in the examined groups, there was no significant variation in the PGA score between groups. Most patients in both groups showed poor status, with non-significant disparity among both groups. However, after both procedures, there was a substantial increase in PGA score in group I compared to group II. Most cases in group I showed excellent and good improvement compared to poor and moderate improvement in group II, with non-statistically significant differences between them.

The Attwa trial showed that the incidence of repigmentation with varying grades and no scarring was much higher when needling was paired with 5-FU compared to needling alone. Lesions caused by Vitiligo are pigmented in one of two ways: follicular (small, brown, perifollicular macules that grew and aggregated) or by pigment spreading outward from the lesion's borders for a millimeter or two (perilesional hyperpigmentation).[15]

In addition to the 5-FU solution, tacrolimus ointment, which Malik also used to treat his Vitiligo, is effective in combination with needling, albeit it is more expensive.[16]

Nilforoushzadeh et al. revealed that a few speculated processes may be responsible for repigmentation following needling. These mechanisms involve trauma-induced inflammation, which leads to the migration of keratinocytes along with melanocytes during the healing phase; an influx of cytokines, which leads to the stimulation of melanocytes in the periphery of the patch or outer root sheath of pigmented hair; and mechanical migration of melanocytes, which involves physically moving melanocytes with the needle from the pigmented area of the hair.[17]

On the other hand, Mohamed et al.utilized a carbon dioxide laser instead of microneedling by dermapen mixed with topical 5-FU with outcomes of 49.8%; our study revealed better outcomes with less cost and shorter downtime.[5]

Anbar et al. demonstrated that utilizing combination therapy with ER: YAG laser with 5-fluorouracil followed by NB-UVB therapy resulted in a significant response (≥ 75%) in almost half of the lesions (49.8%, 476 lesions). They found that vitiligo lesions on the dorsum of the hands and feet may be regulated entirely by the end of treatment after five months, which was significantly more significant than the results of many other studies.[18]

The research conducted by Weshahy et al. indicates that a combination of ablative fractional CO2 laser and topical application of 5FU is effective in treating acral Vitiligo. Improvements in the VESTA score and repigmentation, as judged by two blinded investigators utilizing a 5-point scale examination of patient pictures, and patient satisfaction all attested to the treatment's success.[12]

According to Chhabra, 5-FU also causes colonization of melanocytes in the vitiliginous epidermis by promoting the separation of epidermal melanocytes from the surrounding pigmented skin and enhancing their migration toward the affected areas for two to three millimeters following epithelialization of the epidermis. This process is believed to induce melanocyte colonization in the vitiliginous epidermis.[19]

In addition, Mohamed et al. cleared that the death of pigment cells causes Vitiligo, and 5-FU competes with deoxyuridine and its derivatives for the enzyme thymidylate synthetase, damaging an inhibitory agent or cells in the epidermis or dermis in the process.[5]

Regarding Makkiresearch, the development of ablative fractional CO2 and fractional

photothermolysis make it simpler to induce rapid healing of ablated skin with little side effects. In contrast to conventional laser resurfacing, the neighboring normal tissue supplies a reservoir of live tissue, allowing for fast epidermal restoration.[13]

In addition, the thermal effect induced by a CO2 laser is greater than that of an Er: YAG laser. Numerous studies have proposed Narrowband UVB (NB-UVB) monotherapy, sun exposure, combined NB-UVB phototherapy, and topical clobetasol propionate as potential treatments for Vitiligo. Ablative fractional CO2 and the concept of fractional photothermolysis have made it less challenging to promote rapid healing of ablated epidermis with minimal downtime.[14]

The limitation is that there are uncooperative patients who refused to consent to the Sharisharehe study.

5. *Conclusion*

We concluded that using a combination of CO2 laser or microneedling with 5-fluorouracil is a more prosperous and safe approach for treating vitiligo than using each of these treatments alone. This procedure offers cases a new therapeutic window and has shown encouraging outcomes.

5.1 Recommendations

We recommend considering these findings to achieve better outcomes for vitiligo patients and paying attention to this fact while outlining the recent guidelines for managing these patients. In addition, further studies must be done to analyze all aspects of this issue.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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