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RESEARCH ARTICLE

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Microneedling along Topical 5-Fluorouracil in the Treatment of Stable Resistant Vitiligo

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ABSTRACT

Background: Vitiligo poses a challenge to all dermatologists with a major socio-psychological concern. Despite the available various numerous treatment modalities, a unique innovative universally reliable therapeutic modality is yet to emerge due to the disparity of response among different patients.

Objective: The aim of this study is to assess the safety and efficacy of microneedling along with the application of topical 5-fluorouracil in the treatment of stable localized vitiligo. Research Methods: This study is intended to be a quasi, nonrandomized experimental design with the inclusion of 28 patients having localized stable vitiligo based on convenient sampling methods with certain inclusion criteria. Microneedling along with the application of topical 5-FU will be performed once every 2 weeks for a total duration of 6 months. The Epi-data software will be used for data collection, analysis and interpretation. Excellent results in terms of 50-75% repigmentation of the initial vitiligo macule/patch is expected with the 6 months period based on a previous recent study conducted within a similar scope. No major ethical concerns are associated with this study. Funding is required in regards to covering the expense of the instrument (i.e. derma roller) and medication (topical 5-FU cream/solution) used.

Results: At the end of 4 weeks, Grade I re-pigmentation was noted in approximately 46% and Grade II repigmentation was seen in 46% whereas 8% showed Grade IV re-pigmentation. There was a statistically significant difference in the proportion of re-pigmentation grade between week 2 and week 4 (McNemar-Bowker test, P= 0.046). Discussion: We can say that needling with topical application of the 5-FU solution is a simple, cost-effective, and safe modality without the need of extensive surgical instruments and minimal side effects. It can be used as an alternative or additive method before, or in combination with other approved methods for stable vitiligo.

Conclusion: We can say that microneedling with topical application of the 5-FU solution is a simple, cost-effective, and safe modality without the need of extensive surgical instruments and minimal side effects. It can be used as an alternative or additive method before, or in combination with other approved methods for stable vitiligo.

ARTICLE HISTORY

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KEYWORDS

Vitiligo, Derma Roller, 5-Fluorouracil

Introduction and Literature Review

Introduction

Vitiligo is an acquired depigmenting disorder of the skin, in which pigment-producing cells (melanocytes) are progressively lost due to an autoimmune destruction. It appears as milky-white patches of the skin and causes significant cosmetics and social concerns.

The prevalence of vitiligo in Oman has been reported as 2.13% of the total Omani population attending Dermatology clinics in North Al Batinah Governorate over a period of 4 years between 2010-2013.

The available therapeutic options include both nonsurgical and surgical varieties. Nonsurgical options include topical corticosteroids, calcipotriols or tacrolimus. In addition to psoralen and ultraviolet A (PUVA), narrow-band ultraviolet B (NBUVB) and immunosuppressants. Surgical options include skin grafting, autologous culturing of melanocytes, or epidermal suspension transplantations. Despite the variety and availability of numerous treatment modalities, a single reliable therapeutic modality is highly needed to the variations in response among different patients.

Microneedling followed by the application of a topical 5% 5-fluorouracil (5-FU) is a novel and extremely understudied modality of treatment. Several reports have been surfacing

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regarding the efficacy of dermabrasion combined with 5-FU in the treatment of vitiligo.

Hence, this study was warranted to assess the effectiveness of microneedling coupled with 5-FU in the treatment of stable localized vitiligo.

Literature Review

While, multiple reports have emerged implying the hopeful and astonishing results of this treatment, our literature review revealed only a single recent research published in the Journal of Dermatology and Dermatologic Surgery (July, 2021). The study concluded that needling with the topical application of 5-FU solution is a simple, cost-effective and safe modality that can be used as an alternative treatment for stable localized vitiligo.

No such local or even regional studies have been reported.

The Gap and Relevancy of the Study

The Gap

We are not satisfied with the previous studies/current knowledge due the following rationale:

- Just a few studies till date related to our specific question worldwide, and hence the literature is not sufficient.
- Previous studies addressed different groups/settings, hence, the need for a local more specific study is warranted.

The Relevancy (Significance) of the Study

This study might have a great impact on several aspects; it might change the clinicians' options regarding the treatment of vitiligo. Might affect the decision makers towards implementing a simple and cost-effective modality. And last but not least, might rapidly restore the life quality of patients with such a safe, relatively fast and effective treatment.

Objectives and Hypothesis of the Study

Objective

This study is aimed to assess the safety and efficacy of microneedling along 5% 5-fluorouracil in the treatment of stable localized vitiligo among vitiligo patients attending Sultan Qaboos University Hospital in the period between December 2022 to June 2023.

Study Hypothesis

Microneedling with topical 5% 5-FU is a simple, cost-effective and safe treatment modality in stable localized vitiligo.

Feasibility of the Study

This study is feasible in the sense of:

- Availability of participants and willingness to participate.
- Attainable capabilities compared to sample size required.
- Highly qualified training & commitment of research team members.
- Affordable needed resources/personnel/funding.
- Sufficiency of time.
- Nill major ethical concerns.

Research Design and Methods

Study Design

- Quasi-experimental design (time series; pre, 3 months & 6 months).

Characteristics of Study Area and Target Population

- This study will be conducted in the Dermatology clinic of the Sultan Qaboos University Hospital which is a tertiary care institution.
- The target population of this study includes patients with stable localized vitiligo with the following inclusion criteria:

1. The maximum number of patches in each patient is 5.
2. The patches should be stable, i.e. should not have shown any change in color/size During the last 6 Months.
3. The size of an individual patch should be < 10 cm in diameter.
4. Patient must not have undergone any systemic therapy before inclusion in the study.
5. The patches should be free of any active infections at the time of inclusion.
6. Patients who are 18 years of age or older.

Exclusion Criteria Includes the Following:

1. Pregnant and lactating women (as 5-FU is category X).
2. Patients with mucosal vitiligo (poor prognosis).
3. Patients with active infections (microneedling will cause localized pores to the skin).
4. Patients with tendency to develop keloids.

5. Patients with history of koebnerization.

6. Patients with bleeding disorders.

7. Patients with uncontrolled systemic illnesses.

8. Patients with known Dihydropyrimidine dehydrogenase (DPD) deficiency.

*DPD deficiency is a condition in which the body cannot break down the nucleotides, thymine and uracil. Most people have no obvious signs or symptoms, but some develop serious neurological problems as infants. Those signs and symptoms may include seizures, intellectual disability, microcephaly, hypertonia, delayed motor skills and autistic behavior. Even though, the systemic absorption of topical 5-FU is far less than the intravenous administration (as used in chemotherapy), some case reports were indicating that patients with profound DPD deficiency developed neurotoxicity, GI and hematologic toxicity post topical application of 5-FU.

As a precaution, patients who are older than 18 years of age will be allowed to be involved in the study and some screening questions to rule out any DPD deficiency symptoms will be included in the consent form.

Sampling

- A sample from the target population will be studied.

- Sample size - The estimated sample size is 28. The estimation was based on the statistical test, One-way repeated measures ANOVA with anticipated medium effect size of '0.25' (Cohen's f). The number of groups was '1' and the number of outcome measurements was '3' (pre-intervention, post-intervention at 3 months, and post-intervention at 6 months). The anticipated correlation coefficient among repeated measures was '0.50'. The type I error alpha was set at 5% and the power was set at 80%. The calculation was done in G*Power version 3.1.9.7.

- Sampling method: convenient sampling.

Variable Definitions and Measurements

- The size of the vitiligo patch will be measured 3 times: 1. Pre (as a baseline). 2. After 3 months of study commencement. 3. And after 6 months.

- The measurement is taken as percentages of repigmentation and converted into grades whereas: Grade I (G1) < 25% repigmentation (poor), Grade II (G2) 25%-50% repigmentation (fair), Grade III (G3) 50%-75% repigmentation (good), and Grade IV (G4) > 75% repigmentation (excellent).

Details of the Treatment Modality:

1. Route of treatment administration: topical.

2. Dose: About 1 ml of 5-FU solution (50 mg/ml) available in the form of ampules was applied over 1 cm2 area of the patch.

3. Dose interval: rubbed and massaged into the patch for 2 minutes.

4. Dose frequency: biweekly.

5. Treatment period: a total of 6 months.

- New apparatus to be used include a derma-roller with needle size of 1.5 mm.

Data Collection Tools and Methods

- A data collection sheet will be used.

- Data will be collected in the form of continuous variables as percentages of repigmentation of the initial patch.

- The data will be collected in a prospective manner by qualified trained Dermatologists/Dermatology residents.

- The process of recruitment of the candidates rely on convenient and suitable selection from the patients attending the Dermatology clinic at SQUH and fulfilling the inclusion criteria.

Pilot Study

A pilot study on a smaller number of participants is preferred. That is to further assess feasibility and difficulties.

Data Quality

- The quality of the primary data will be taken by a qualified trained Dermatologist/senior Dermatology resident.

- Furthermore, the quality of the collected data will be subjected to the following to ensure the optimal data quality:

- A portion of the collected data will be re-checked by rechecking the patients' records.

- A continuous supervision of data collectors, to ensure that data collectors are doing right things from time to time.

- Data revision for coding, entry and cleaning will be done prior to analysis.

- Data will be entered using Epi-data software.

- At any time, the data will be digitally saved in at least 2 different devices/flash drives to minimize data loss.

Patient No.	Nationality	Gender	Age	Sites of Vitiligo	Grade of Repigmentation (at week 2)	Grade of Repigmentation (at week 4)
1	Omani	Male	14	Face/neck	Grade 1	Grade 1
2	Omani	Frmale	14	Face/neck	Grade 1	Garde 1
3	Omani	Female	14	Face/neck	Garde 4	Grade 4
4	Omani	Female	13	Face/neck	Grade 2	Garde 2
5	Omani	Male	22	Face/neck	Grade 1	Grade 1
6	Omani	Male	24	Face/neck	Grade 1	Grade 2
7	Omani	Female	27	Face/neck	Grade 1	Grade 1
8	Omani	Male	30	Scalp	Grade 1	Grade 2
9	Omani	Male	33	Trunk	Garde 1	Grade 2
10	Omani	Male	41	Limbs	Garde 2	Grade 2
11	Omani	Female	13	Trunk	Grade 1	Grade 1
12	Omani	Male	46	Trunk	Grade 1	Grade 1
13	Omani	Male	53	Face/neck	Grade 1	Grade 2

Characteristics		n (%)
Gender	Male	8 (62%)
	Female	5 (38%)
Site of vitiligo	Scalp	1 (7.7%)
	Face/neck	8 (61.6%)
	Trunk/abdomen	3 (23%)
	Limbs	1 (7.7%)
Previous treatment	Yes	13 (100%)
	No	0 (0%)
Grades of Repigmentation n (%)	At 2 wks	At 4 wks
G1	10	6
G2	2	6
G3	0	0
G4	1	1

Data Analysis

Epi-data software was used as a statistical program for the analysis of the data. Quantitative variables were represented as means and standard deviation and categorical variables were analyzed in the form of frequency and percentage.

Frequencies

Statistics

Age

N	Valid	13
	Missing	0
Mean	26.46	
Median	24.00	
Std. Deviation	13.56	
Minimum	13.00	
Maximum	53.00	
Percentiles	25	14.00
	50	24.00
	75	37.00

Frequency Table

Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	8	61.5	61.5	61.5
	Female	5	38.5	38.5	100.0
	Total	13	100.0	100.0	

Nationality

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Omani	13	100.0	100.0	100.0

Site of Vitiligo

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Face/ Neck	8	61.5	61.5	61.5
	Trunk	3	23.1	23.1	84.6
	Limbs	1	7.7	7.7	92.3
	Scalp	1	7.7	7.7	100.0
	Total	13	100.0	100.0	

Previous Treatment

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	13	100.0	100.0	100.0

Grade of Re-Pigmentation (at Week 2)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Grade 1	10	76.9	76.9	76.9
	Grade 2	2	15.4	15.4	92.3
	Grade 4	1	7.7	7.7	100.0
	Total	13	100.0	100.0	

Grade of Re-Pigmentation (at Week 4)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Grade 1	6	46.2	46.2	46.2
	Grade 2	6	46.2	46.2	92.3
	Grade 4	1	7.7	7.7	100.0
	Total	13	100.0	100.0	

Grade of Re-Pigmentation (at Week 6)

	Frequency	Percent	
Missing	System	13	100.0

Crosstabs

Grade of Re-Pigmentation (at Week 2) * Grade of Re-Pigmentation (at Week 4) Crosstabulation

			Grade of Re-pigmentation (at week 4)			
			Grade 1	Grade 2	Grade 4	Total
Grade of Re-pigmentation (at week 2)	Grade 1	Count	6	4	0	10
		% within Grade of Re-pigmentation (at week 2)	60.0%	40.0%	0.0%	100.0%
	Grade 2	Count	0	2	0	2
		% within Grade of Re-pigmentation (at week 2)	0.0%	100.0%	0.0%	100.0%
	Grade 4	Count	0	0	1	1
		% within Grade of Re-pigmentation (at week 2)	0.0%	0.0%	100.0%	100.0%
Total		Count	6	6	1	13
		% within Grade of Re-pigmentation (at week 2)	46.2%	46.2%	7.7%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
McNemar-Bowker Test	4.000	1	.046*
N of Valid Cases	13		

There was a statistically significant difference in the proportion of re-pigmentation grade between week 2 and week 4 (McNemar-Bowker test, P= 0.046).

Ethical Considerations

- This study was granted ethical approval and permission from Sultan Qaboos University Hospital to start the study.
- We acknowledge sticking to local and international ethical standards in this research project.
- An informed consent is needed for the participation in this study, including the use of any relative personal information (such as sex, age, …etc) with patients' pictures (given that their confidentiality and anonymity will be maintained by withholding any clinically irrelevant personal identifying data from publication) for publication purposes (A consent form is enclosed with the proposal).
- Emphasis on the respect of participants and safeguarding their dignity, and rights and freedom to participate or withdraw.

In this Experimental Study

- The benefit expected is far over the expected harm thru what is already known about the intervention. While, the benefit of microneedling coupled with 5-F, as this study is trying to prove and based on the previous studies done within the same scope, is the relatively rapid, safe, cost-effective and excellent response in terms of the repigmentation of the vitiligo macules/patches. On the other hand, the predictable side effects of microneedling coupled with topical 5-FU may include the following:
- Localized and temporarily to area of treatment limited to: pain, erythema, irritation, burning, pruritus and occasionally, allergic contact dermatitis.
- The risk of adverse effects and methods of testing, recording and reporting them, and provisions for dealing with complications.
- Other modalities of treatment will be withheld during the study to exclude any confounding effects.
- State any conflicts of interests in carrying out this project (if any) and sources of funding if applicable.
- Describe potential direct benefits of the research to participants, institutions and/or communities (incentives, capacity building …etc.).

Results Dissemination

- The data will be disseminated to local authorities and international audience in the form of local/international presentations and journal publications.

Limitations and Strengths of the Study

Limitations and Difficulties of the Study

- Expected difficulties in data collection may include unreliable history/information given by the patient.
- Some of the social constraints expected could be unwillingness or refusal to take pictures of the skin lesions and refusal for publication.
- The needed funds are calculated based on the best predictable process and outcome, that may be altered depending on the progress of the study.
- Dedicated time and efforts must be given by the both the researchers and the patients themselves.
- Explain how you will deal with them if possible.

Strengths

- The 1st Quasi-study conducted regionally using a dermaroller.
- Safe and tolerable technique.
- Does not require much expertise or expense.

Declaration

I agree to submit this final proposal draft for approval and I will have full responsibility to manage the project and to follow up various activities in order to finish it in time. I will ensure that the research will not deviate from the protocol described. If significant protocol amendments are required as the research progresses, I shall submit these to the Research Review Committee for approval. Also, I will be responsible to provide progress reports and final report for my program research subcommittee for revision before final dissemination

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