Original Article

Effect of Topical 5% 5-Fluorouracil with Microneedling in Vitiligo Patients as an Additional Modality to Standard Treatment at Tertiary Care Hospital

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Abstract

Background: Vitiligo is an inveterate disease of great aesthetic concern presenting with depigmented macules and patches. It is often incorrigible to medical treatment. **Aim:** To study the clinical profile of vitiligo patients and evaluate the effect of 5% 5-fluorouracil (5-FU) cream with microneedling. **Materials and Methods:** This observational analytical study was conducted from November 2019 to July 2021. A total of 33 adult vitiligo patients were treated with oral mini-pulse (dexamethasone) therapy and topical corticosteroid (clobetasol propionate 0.05%). Patient's total number of vitiligo lesions with <10-cm size were counted and half of the lesions were treated with 5-FU + microneedling (Group A), while a remaining number of lesions were not treated with 5-FU + microneedling (Group B). In the case of the odd number of lesions, the total number of lesions minus one was considered and then divided into equal numbers for treatment. The procedure was performed every 2 weeks for 3 months. Clinical improvement was assessed monthly till 6 months by serial clinical photographs and grading scores. **Results:** Initiation of repigmentation started in the first month in Group A, whereas in Group B, it was seen in the second, which was statistically significant ($P < 0.0001$). Excellent improvement (>75% repigmentation) was noted in Group A as compared to Group B at the end of 6 months ($P < 0.0001$). **Conclusions:** Needling with 5% 5-FU appears to be a simple, safe, and effective treatment in vitiligo. It can be used in poor responders to conventional therapy.

Keywords: *Microneedling, 5% 5-flurouracil, vitiligo*

Introduction

Vitiligo is an acquired, progressive depigmenting disease that results from the loss of melanocytes within the interfollicular and/or intrafollicular area. Inheritance of vitiligo is polygenic and etiology is complex.[1] Vitiligo occurs worldwide with a gross prevalence of 1% and positive family history vary from 6.25 to 18%.[2] Vitiligo has been assorted into two major forms, namely, segmental vitiligo (SV) and nonsegmental vitiligo.[3]

Various treatment modalities include medical therapy as the first line, phototherapies as the second line, and surgical therapies like grafting and microneedling as the third line.[2] This study was conducted to review the clinical profile of vitiligo and to evaluate the efficacy and safety of the additional management modality of 5-fluorouracil (5-FU) with microneedling in vitiligo patients at tertiary center.

Materials and Methods

Study design

This was a hospital-based observational analytical comparative study conducted in the outpatient department of dermatology from November 2019 to July 2021. Clearance for the study was obtained from the institutional ethics committee [reference no. 77 (26/11/2019)].

Sample size

The sample size was calculated by applying the formula for comparative studies.[4]

$$N = (SD_1^2 + SD_2^2)^2 (Z_{1-b} + Z_{1-a/2})^2/d^2$$

where N = sample size, SD_1 = standard deviation of group 1, SD_2 = standard deviation of group 2, Z_{1-b} = desired power, $Z_{1-a/2}$ = critical value and standard value for the corresponding level of confidence, and d = effect size.

Based on the previous study,[5] the sample size was calculated as 33 patients.

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Study subjects

A total of 33 adult patients with vitiligo attending the outpatient department of dermatology during the study period excluding the patients with vitiligo patches on mucous membrane, Koebner phenomenon, keloid or hypertrophic scar tendency, and other uncontrolled systemic illnesses were included in the study. They were asked about the duration of the disease, total number of patches, and presence of white hair. Informed written consent was obtained from each patient.

Study intervention

All patients were treated with oral mini-pulse (dexamethasone) therapy and topical corticosteroid (clobetasole propionate 0.05%) as per standard guidelines. The patient's total number of vitiligo lesions with <10-cm in size were counted. Half of the lesions were treated with a combination usage of 5% 5-FU + microneedling along with standard treatment (Group A), while the remaining number of lesions were treated with standard treatment alone (Group B). In case of an odd number of lesions, the total number of lesions minus one was considered and then divided into equal numbers for treatment.

Under aseptic precautions, microneedling was done with the help of a 1.5-mm size needle dermaroller in different directions after local anesthesia. Visible pinpoint bleeding in the entire lesion is the end point for the roller procedure. Immediately after this procedure, 5% 5-FU cream was applied in a thin layer and occlusive dressing was done for 12 h.

Follow up

All patients were followed up every 15 days for the next 6 months and microneedling + 5-FU was repeated every 15 days on previously treated lesions for 3 consecutive months only.

Repigmentation was assessed according to the percentage of repigmented area as grade 0 (no response), grade 1 (poor, <25%), grade 2 (good, 25–50%), and grade 3 (very good, 50–75%), and grade 4 (excellent, >75%). G3 and G4 grades were considered as the desirable outcomes.

Statistical analysis

All the data were compiled and entered in Microsoft Excel and analyzed by using STATA 14.2. Categorical variables were expressed in frequency and percentages. Continuous variables were presented as Mean ± SD. Mann–Whitney *U* (two-sample Wilcoxon rank-sum) test was used to compare the response of combination usage of 5% 5FU + microneedling along with standard treatment group (group A) and standard treatment alone group (group B). $P < 0.05$ was considered statistically significant at the end of the study.

Results

Both Groups A and B were exact matches in the context of age, sex, and duration of disease. Out of 33, a total 30 patients had completed 6 months follow-up. Three patients did not come for follow-up after second, third, and fifth month, respectively. We found vitiligo to be more prevalent in females comprising 21 (63.64%) patients. The most common morphological type in our study was vitiligo vulgaris (22 of 33, 66.67%) followed by acral vitiligo (8 of 33, 24.24%) and SV (3 of 33, 9.09%). More details regarding the clinical characteristics of both the groups are mentioned in Table 1.

Figure 1 shows the response to treatment in both the groups at the end of the study period. Group A showed 9 (30%) patients with good, 20 (66.67%) patients with very good, and 1 (3.33%) patient with excellent response [Figures 2 and 3]; Group B showed 5 (16.67%) patients with poor [Figures 4 and 5] and 25 (83.33%) patients with good response; and neither very good nor excellent response was observed in Group B and no poor response in Group A.

At the end of 6 months, a statistically significant difference was observed between the two groups with better outcomes in Group A ($P < 0.05$).

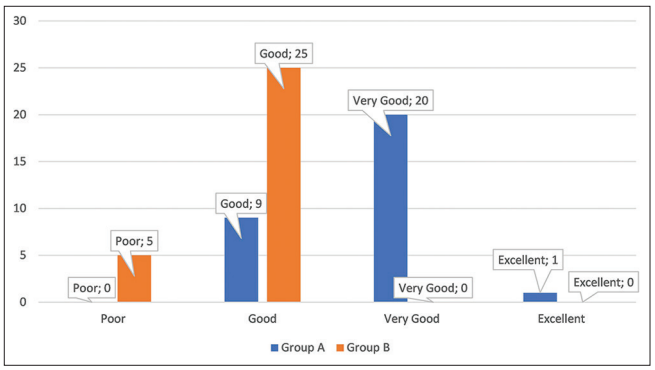

Figure 1: Response of treatment in group A and group B at end of 6 months follow-up. X-axis: Response to treatment, Y-axis: Number of patients

Table 1: Clinical details of the patients

Clinical data	Demographic details
Gender distribution	Male 12 (36.36%)
	Female 21 (64.64%)
Age in years (mean)	33.52 years
Duration of disease (mean)	4.49 years
Type of vitiligo	Vitiligo vulgaris 22 (66.67%)
	Acral vitiligo 8 (24.24%)
	Segmental vitiligo 3 (9.09%)
Severity of pigment loss	Moderate – 27 (81.82%)
	Severe – 6 (18.18%)
Presence of leukotrichia	6 (18.18%) patients
Number of lesions in each patient	<5 lesions – 16 (48.49%)
	5–10 lesions – 15 (45.45%)
	>10 lesions – 2 (6.06%)

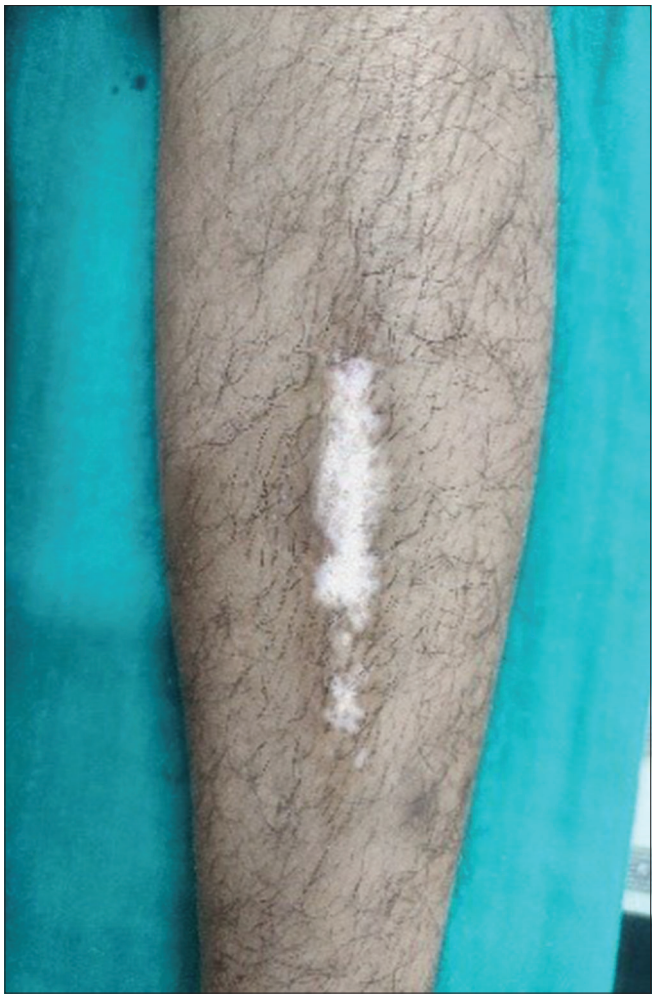

Figure 2: Patient of group A at the start of the study

Erythema and crusting [Figure 6] were seen in 7 (21.21%) and 1 (3.03%) samples in Group A patients, while Group B samples are free from any adverse effect. Koebner's phenomenon was not seen in any patient. Site-wise analysis revealed that excellent response was most often seen in patches over the trunk followed by head and neck and limbs in both the groups. None of the lesions in Group B showed excellent response [Tables 2 and 3].

Discussion

Vitiligo is a major socio-psychological problem, especially in dark-skinned individuals.[6] It continues to be challenging, in spite of the availability of multiple therapeutic modalities. As curative treatment is not available, current treatment modalities are directed toward stopping the progression of vitiligo and achieving pigmentation to repair morphology and functional deficiencies of the depigmented areas. However, no single treatment method has yet been found that is consistently effective with relatively few side effects. Various trials have shown that combined modalities improve the overall effectiveness and time needed to achieve repigmentation reducing the potential adverse effects.[7]

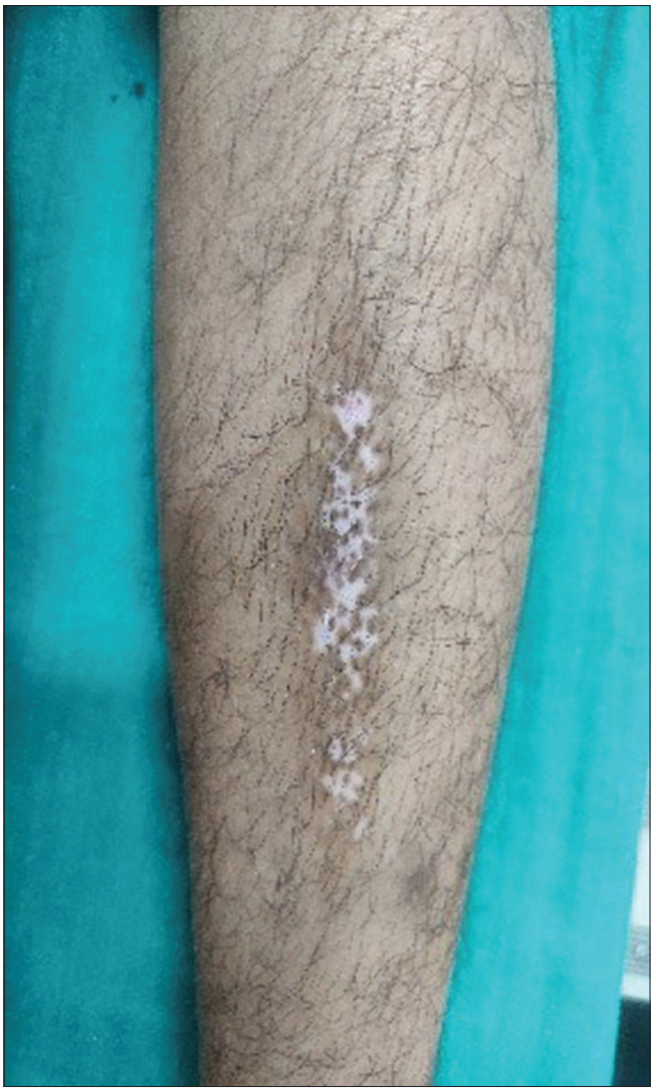

Figure 3: Patient of group A at 6 months follow-up (grade 4 response)

Table 2: Repigmentation response in group A according to site

Response	Head and neck	Upper limbs	Trunk	Lower limbs
Poor (Grade 1)	0	0	1	1
Good (Grade 2)	1	2	5	21
Very Good (Grade 3)	2	9	8	28
Excellent (Grade 4)	0	1	2	2
Total number of lesions	3	12	16	52

Tsuji and Hamada[8] introduced the method of application of 5-FU after therapeutic wounding as the treatment of vitiligo. FU shows selective and differential cytotoxicity toward epidermal cells. Melanocytes are less vulnerable to fluorouracil than keratinocytes. The mechanism of repigmentation suggested that 5-FU causes overstimulation of melanocytes of follicles, which migrates during epithelialization and induces pigmentation.[9] Needling induces a strong inflammatory response and local edema,

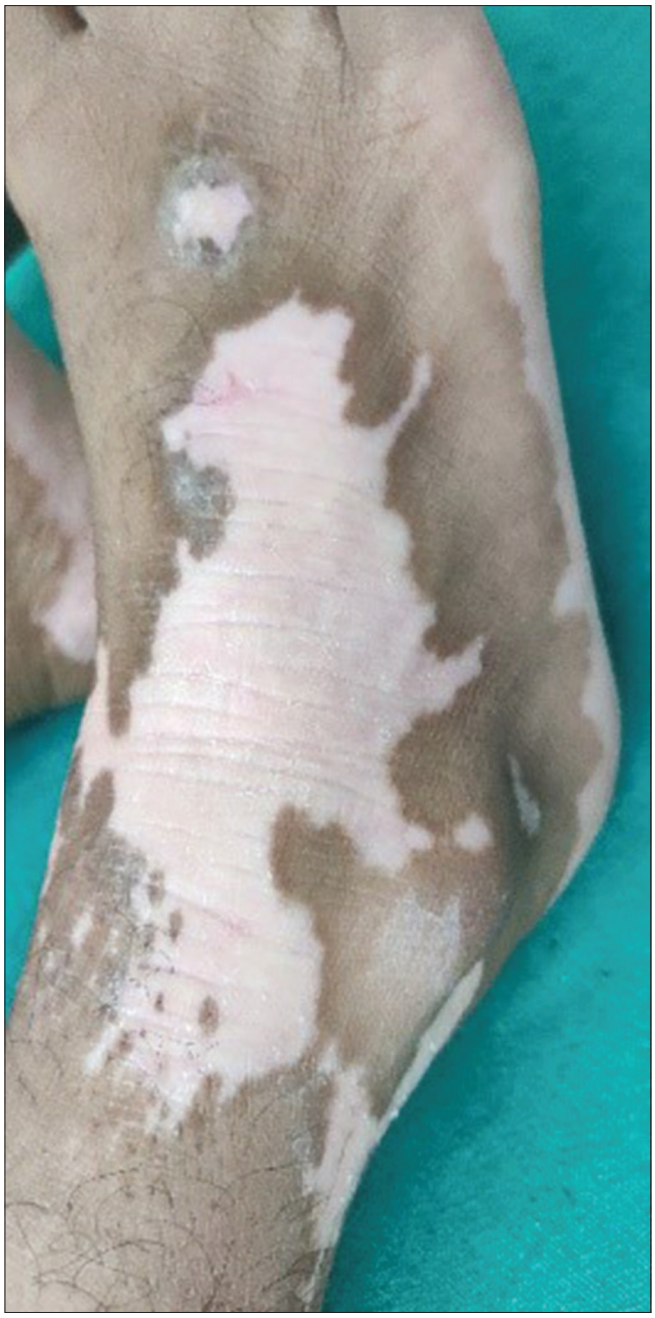

Figure 4: Patient of group B at the start of the study

leading to increased intercellular spaces of the basal layer. Active melanocytes migrate from the pigmented epidermis through these spaces. The inflammatory mediators such as leukotrienes C4 and D4 and matrix metalloproteinases from keratinocytes help in melanocyte migration and proliferation.[10,11]

This work was a comparative study between the efficacy of standard treatment alone and combination usage of 5% 5-FU with microneedling along with standard treatment. The study was also done to determine the additional effect of 5% 5-FU with microneedling on vitiligo lesions.

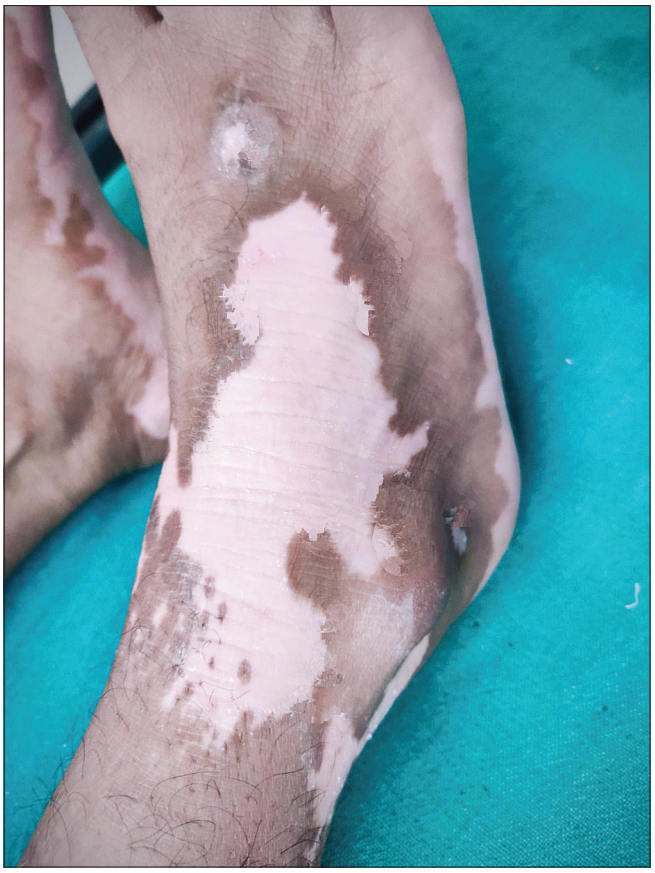

Figure 5: Patient of group B at 6 months follow-up (grade 1 response)

In study done by Zahra *et al*.,[5] Group A was treated with 5% 5-FU cream with microneedling while Group B was treated with only 5% 5-FU cream. A study done by Asker *et al*.[12] compared two groups. One was treated with 5% 5-FU cream only, while another group was treated with 5% 5-FU and sandpaper. A study done by Mina *et al*.[7] did a comparison between the efficacy of microneedling combined with 5-FU vs microneedling with tacrolimus in the treatment of vitiligo. A study by Santosh *et al*.[13] was done to observe repigmentation after applying 5% 5-FU after microneedling with a 26G needle. An open, nonrandomized, single-arm study was done by Shashikiran *et al*.[14] to observe the safety and efficacy of needling followed by topical 5% 5-FU application on patches of vitiligo. This procedure was done every 15 days for 3 consecutive months similar to our study.

In our study, the total number of vitiligo lesions was 176. Out of the total lesions, 6 (3.41%) lesions were present on the head and neck region, 27 (15.34%) lesions were present on the upper limbs, 32 (18.18%) lesions were present on the trunk, and 111 (63.07%) lesions were present on lower limbs.

Vitiligo vulgaris was the most common type to be found in the present study, having 22 (66.67%) patients. Eight (24.24%) patients had acral vitiligo, while only

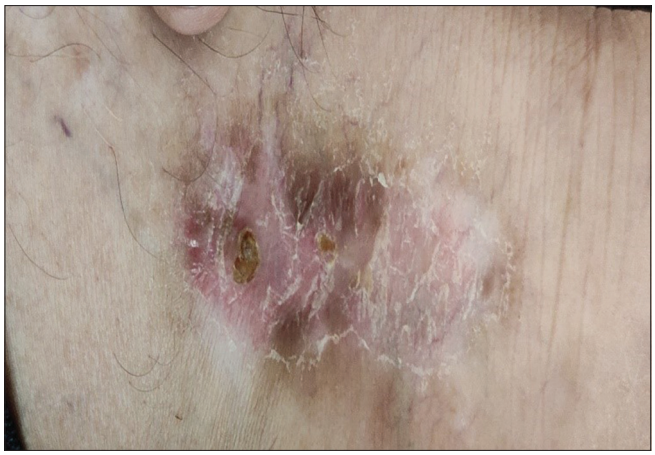

Figure 6: Crusting in a patient of group A

Table 3: Repigmentation response in group B according to site

Response	Head and neck	Upper limbs	Trunk	Lower limbs
Poor (Grade 1)	2	9	12	47
Good (Grade 2)	1	5	4	10
Very Good (Grade 3)	0	1	0	2
Excellent (Grade 4)	0	0	0	0
Total number of lesions	3	15	16	59

3 (9.09%) patients had SV. Other vitiligo types were not observed in our study.

A study done by Abdelwahab *et al*.[15] showed 27 (90%) patients having vitiligo vulgaris, 2 (6.67%) patients having acral vitiligo, and 1 (3.33%) patient had vitiligo universalis. A study done by Zahra *et al*.[5] described the distribution of patients according to different types of vitiligo. Out of total 60 patients, 37 (61.67%) had vitiligo vulgaris, 12 (20%) had focal vitiligo, 5 (8.33%) had SV and 6 (10%) had acral vitiligo. These findings were similar to our study.

A study done by Shashikiran *et al*.[14] reported that out of 39 patients, 23 (58.97%) had vitiligo vulgaris, 13 (33.33%) had acrofacial, and 3 (7.70%) had focal vitiligo. A comparative study done by Mina *et al*.[7] reported that 15 (60%) patients had vitiligo vulgaris and 10 (40%) patients had acral vitiligo. Other types of vitiligo were not observed in their study.

Majority of patients – 27 (81.82%) – did not present with leukotrichia in our study, while 6 (18.18%) patients presented with this particular feature. A study done by Zahra *et al*.[5] also described similar findings with 49 (81.67%) patients without leukotrichia, while 11 (18.33%) had it.

In our study, 66.67% of patients show very good (grade 3) response, 30% patients show good response (grade 2), and 3.33% of patients show excellent response (grade 4) in Group B which was treated with 5% 5-FU in addition to standard therapy. A study done by Shashikiran *et al*.[14] showed 49% samples with excellent (grade 4), 26% with very good (grade 3) response, 11% with good (grade 2) response, and 14% with poor (grade 1) response. A study done by Ghiya *et al*.[6] showed 60% patients with excellent (grade 4), 12% with very good (grade 3), 20% with good (grade 2), and 8% with poor (grade 1) response. A comparative study done by Mina *et al*.[7] described 48% of patients with excellent (grade 4), 4% with very good (grade 3), 20% with good (grade 2), 20% with poor (grade 1), and 8% with no (grade 0) response. Another comparative study done by Zahra *et al*.[5] showed that 47% patients with excellent (grade 4), 46.2% patients with very good (grade 3), 6% patients with good (grade 2), and only 0.8% patients with poor (grade 1) response. All studies mentioned here showed better repigmentation with very good and excellent response, but our study found most responses were very good and good.

In our study, 21.21% of patients treated with 5-FU showed erythema and 3.03% of patients showed crusting as side effects. A study done by Ghiya *et al*.[6] showed 12% of patients with crusting and 28% of patients showed hypertrophic scarring as side effects. Study done by Shashikiran *et al*.[14] showed 52% with erythema and 6% patients with ulceration as side effects. A comparative study done by Zahra *et al*.[5] reported 10.26% of samples with pain, 17.09% with erythema, 8.55% with itching, and 1.17% with ulceration as side effects, while 62.93% of samples with no side effects which was comparable to our study also noted 75.76% with no side effects. So, overall no major side effect was observed in our study.

Loss of pigmentation was not seen in any of our patients probably due to the short follow-up period after the intervention. No systemic side effect was reported in our study, thereby making use of topical FU along with needling safe and effective therapeutic modality in the treatment of vitiligo.

Limitations of our study included an unblinded design and a short follow-up period. This study also did not evaluate the efficacy of the intervention on mucosal vitiligo.

Conclusion

We found that needling followed by topical application of 5-FU has much higher efficacy than 5-FU alone in vitiligo. It is a useful therapy in poor responders to conventional therapy. However, the stability of repigmentation has to be analyzed with a longer period of follow-up.

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Conflicts of interest

There are no conflicts of interest.

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