

Comparing the efficacy of topical clobetasol 0.05% plus 5FU 5% cream vs. topical clobetasol 0.05% alone in treatment of vitiligo

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BACKGROUND: Vitiligo is an acquired, autoimmune melanocytic disorder characterized by circumscribed depigmented macules and patches. It affects approximately 0.5-2% of the general population worldwide. Many medical treatments have been attempted with partial success, but there has been no previous trial on the combination of topical 5-fluorouracil (5FU) 5% and clobetasol. **METHODS:** The aim of this study was to evaluate and compare the therapeutic efficacy of topical clobetasol (as a standard method for treatment of vitiligo) versus a combination of topical clobetasol + 5FU. In this double-blind clinical trial study, 45 patients who had at least two vitiligo patches were treated with topical clobetasol on one side of the body, and with a combination of clobetasol and 5FU on the other side. Treatment was repeated every other day, once a day, for three months. At the end of the treatment, patients were visited again to be evaluated for the therapeutic efficacy of the drugs. **RESULTS:** Paired t-test revealed a significant improvement in both sides (the right side which was treated with 5-FU+clobetasol and the left side which was treated with clobetasol alone). Therefore, both drugs seem to have been effective in the improvement of vitiligo ($p < 0.0001$). Comparing the percentage of improvement in the lesion size, there was a statistical difference between the two groups (right side = $38.1 \pm 4.3\%$ and left side = $24.2 \pm 3.3\%$; $p < 0.0001$). **CONCLUSIONS:** Adding topical 5FU to clobetasol increases its efficacy in treatment of vitiligo without significant side effects. **KEYWORDS:** Vitiligo; Therapy; Clobetasol; 5-Fluorouracil

BACKGROUND

Vitiligo is an autoimmune disorder of melanocytes, characterized by circumscribed depigmented macules.^[1] It affects approximately 0.5-2% of the world population. Although the onset may occur at any age, it is usually in the second and third decades of life^[2] while 50% of the patients are younger than 20 years old.^[3]

The clinical presentations of vitiligo include generalized, segmental, focal, and acrofacial subtypes. The main mechanism is destruction of melanocytes by an autoimmune T-cell lymphocytic attack.^[4] The strongest association of vitiligo is with thyroid diseases (hyper or hypothyroidism).^[5,6]

Another possible mechanism for vitiligo is the neurogenic hypothesis which suggests nerve endings in the skin to release chemicals that are toxic for melanocytes.^[7,8]

The diagnostic criteria for vitiligo include the patient's age, distribution of lesions, and marginal hyperpigmentation.^[9]

Considering the serious psychological impacts of vitiligo which extensively affect the social life of the patients, the disease needs to be treated.^[10,11]

Several treatment modalities, including psoralen plus ultra-violet A (PUVA), narrow band ultra-violet B (NBUVB), corticosteroids, topical calcipotriol, tacrolimus, and autologous melanocyte grafting, are available.^[12-17] However, they have certain side effects and variable results.^[18,19] Nearly 30% of patients have refractory vitiligo.^[20]

As a chemotherapeutic and immunomodulatory drug, 5-fluorouracil (5FU) has been previously used as local treatment in vitiligo but the results were unsatisfactory. Dermabrasion followed by application of 5FU has been found to be effective but with side effects such as local infection and koebnerization.^[21]

Previous studies have used 5FU in the treatment of many skin disorders such as actinic keratosis, epithelial neoplasms,^[22] psoriatic plaques,^[23] Bowen's disease,^[24] and porokeratosis.^[25] In those cases, 5FU acts as an antimetabolite interfering with DNA synthesis by inhibiting thymidylate synthase activity.

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Thymidylate synthase catalyzes the methylation of deoxyuridylic acid to thymidylic acid, a DNA precursor. The most frequently encountered local adverse reactions were pain, pruritus, hyperpigmentation, and burning at the site of the application.^[26] Today, the use of 5FU in combination with other treatment modalities improved vitiligo lesions and decreased the treatment duration.^[27-30] However, 5FU in combination with dermabrasion was ineffective in treatment of segmental vitiligo which has different mechanism of pathogenesis.^[31]

There is no previously published trial on the combination of topical 5FU and clobetasol in vitiligo. Since adding 5FU to other treatment modalities has improved vitiligo lesions, decreased the treatment duration, and increased patients' compliance, the aim of this clinical trial was to evaluate the efficacy and safety of such combination compared with clobetasol alone in treatment of some subtypes of vitiligo.

METHODS

During October 2009 to September 2011, this double-blind clinical trial was initiated with 50 patients. Finally, 45 patients with at least two patches of vitiligo on their bodies completed treatment modality. One case dropped from the study due to pregnancy, two cases due to migration and two cases were not willing to continue the study. The included subjects were vitiligo patients attending the outpatient clinics of Isfahan University of Medical Sciences (Isfahan, Iran).

This study was initially approved by the Ethics Committee of Isfahan University of Medical Sciences (research project and Ethics Committee agreement number: 388456). It was also registered in the Iranian registry of clinical trials (IRCT ID: IRCT201203049198N2).

Inclusion criteria were having at least 2 lesions on the body, being over 15 years of age, lacking follicular pigmentation (score = 0) or white hair over the lesion, and disease stability within the last 6 months.

Patients were excluded if they had received topical medication for at least 1 month or systemic medication or phototherapy for at least 3 months prior to inclusion, past medical history of liver, kidney, and hematologic disorders, vitiligo lesions on the face, genitalia, or acral areas, pregnancy or lactation, and the segmental subtype. Patients were informed about the study protocol and possible side effects. A written informed consent was taken from all patients before enrollment. Enrolled patients were meticulously examined for

follicular pigmentation and white hair with a Wood's light. The shapes of lesions were copied on a transparent sheet, scanned, and scaled to the real size in AUTOCAD 2008. Lesion sizes were then measured in cm².

Clobetasol 0.05% cream (Daroupakhsh, Iran) and its combination with 5FU 5% cream (Valeant, Switzerland) were dispensed in identical tubes and encoded by the pharmacologist. Each patient was provided with 2 tubes for topical use over the different sides of the body (tube A for the right side and tube B for the left side). Neither the physician nor the patients were aware of the contents of the tubes. The patients were instructed how to apply the drugs. Since clobetasol can induce atrophy, patients were recommended to use the drug every other day, once a day. The patients were advised to report the occurrence of any unwanted side effects (redness, atrophy, burning, itching, and erosion) during the 3-month^[32] course of the study. At the end of the study, patients were evaluated for improvement and side effects. The real sizes of the lesions were evaluated at baseline and the end of the study by Wood's light examination. Changes in size and surface area of the lesions and also perifollicular pigmentation occurrence were measured.

The improvement scoring system based on diffuse pattern change in the size of vitiligo patches included poor response for no improvement, moderate response for improvements < 25%, good response for improvements 25-50%, excellent response for improvements > 50%.

The improvement scoring system based on perifollicular pigmentation ranged from 0 to 3 indicating perifollicular pigmentation in 0%, less than 25%, 25-50%, and more than 50% of the lesion area, respectively.^[19,27,29]

At the end of the study, all the patches were evaluated for perifollicular pigmentation, diffuse pattern change in the size of the patches, and real surface change in cm². Finally, the tubes were decoded by the pharmacist.

The statistical analyses of the results were performed using chi-square test, t-test, and paired t-test in SPSS¹⁸ for Windows (SPSS Inc., Chicago, IL, USA). In this study, the significance level was set at p values of less than 0.05. The whole process of the performed procedure is summarized in a consort diagram in Figure 1.

RESULTS

A total number of 45 patients, 19 men (42.2%) and 26 women (57.8%), completed the study. The mean age of

patients was 32.3 years. The mean duration of the disease was 8.5 years with a minimum of 1 year and a maximum of 40 years.

After the tubes were decoded, it was revealed that tube A which had been used on the right side was the combination of clobetasol and 5FU. Tube B on the other hand, was clobetasol alone and had been applied on the left side. We used group A for the right side and

group B for the left side throughout the article.

There was not any difference in the baseline mean area between left and right sides of the body (group A = $12.7 \pm 2.3 \text{ cm}^2$ and group B = $10.9 \pm 2.3 \text{ cm}^2$; $p = 0.5$).

Paired t-test showed a significant intra-group difference both in both groups and both drugs seemed to be effective in the improvement of vitiligo ($p < 0.0001$).

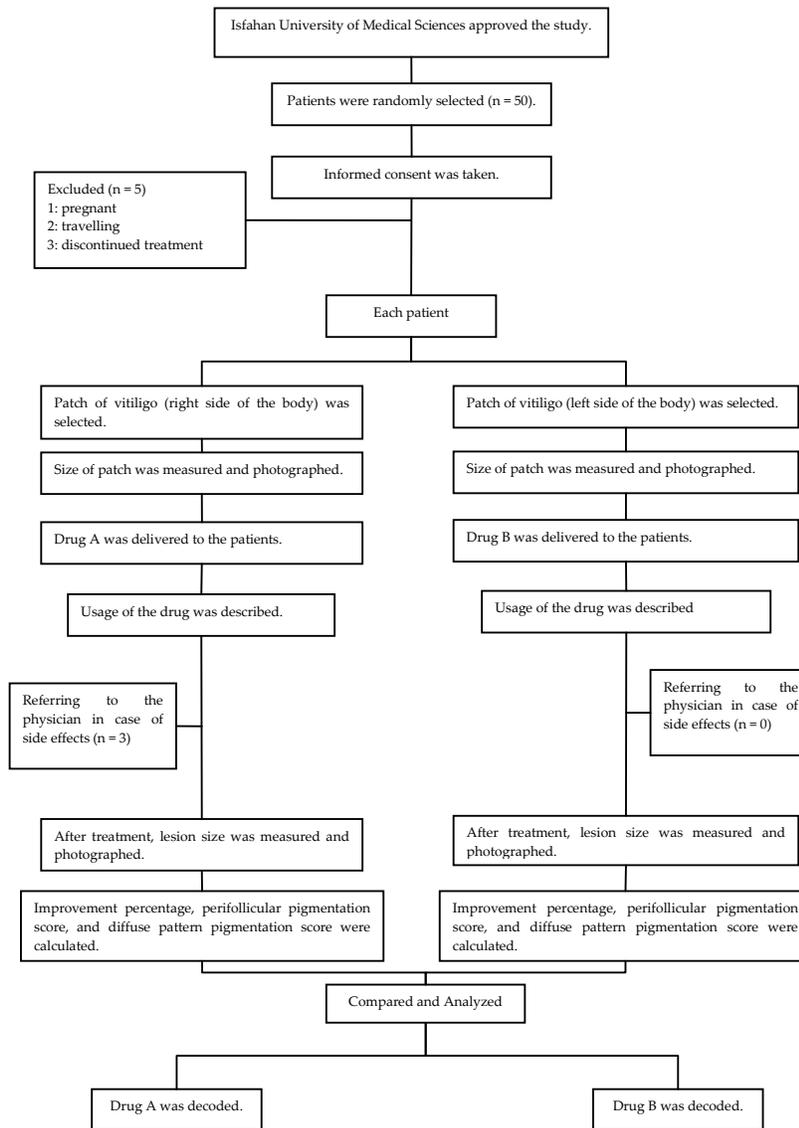


Figure 1. Study procedure

two groups (group A = $38.1 \pm 4.3\%$, group B = $24.2 \pm 3.3\%$; $p < 0.0001$) (Table 1).

Comparing the percentage of improvement in the lesion size revealed a statistical difference between the

Changes in diffuse pattern score are summarized in

Table 2. The excellent response rate was 33.3% in group A and 8.9% in group B which was significantly different according to the chi-square test ($p = 0.01$).

No remarkable improvement was observed in perifollicular pigmentation, i.e. 80% of group A and 91.1% of group B were scored as zero (Table 3).

The repigmentation pattern seemed to be diffuse (88.8% in group A and 84.5% in group B) rather than follicular (20% in group A and 8.9% in group B) in both groups.

Considering the safety profile of the two groups, while no side effects were reported in group B, 3 cases of mild and transient erosion were observed in group A and the patients were advised to stop 3 sessions of drug usage and restart the treatment afterwards. All issues were resolved by this protocol. There was not

any noncompliance and treatment discontinuation due to side effects.

Figure 2 shows the photographs of lesions before and after treatment. All the photos are released under the patient's permission.

DISCUSSION

Vitiligo is a common pigmentary disorder with great sociocultural and psychological importance. It is also a common cosmetic problem. It is still a challenging topic in the field of dermatology. It can make severe psychological distress and induce a severe mental load in the patients' health and quality of life.³³

Corticosteroids are the first documented therapeutic agents for vitiligo treatment. A meta-analysis of existing data showed that corticosteroids and UVB

Table 1. Lesion area before and after treatment and percentage of improvement in Group A (clobetasol plus 5-fluorouracil) and Group B (clobetasol alone)

Method	Before treatment (cm ²)	After treatment (cm ²)	Percentage of improvement (%)	p
Group A	12.7 ± 2.3	9.4 ± 1.9	38.1 ± 4.3	< 0.0001
Group B	10.9 ± 2.3	9.4 ± 2.1	24.2 ± 3.3	

Values are expressed as mean ± standard error.

Table 2. Frequency distribution of diffuse pattern score for Group A (clobetasol plus 5-fluorouracil) and Group B (clobetasol alone)

Method	Poor	Moderate	Good	Excellent
Group A	5 (11.1%)	15 (33.3%)	10 (22.2%)	15 (33.3%)
Group B	7 (15.6%)	17 (37.8%)	17 (37.8%)	4 (8.9%)
p	0.564	0.724	0.178	0.012

Values are expressed as n (%). P values < 0.05 were accepted as significant.

Table 3. Frequency distribution of perifollicular pigmentation score for Group A (clobetasol plus 5-fluorouracil) and Group B (clobetasol alone)

Method	0	1	2	3
Group A	36 (80%)	3 (6.7%)	6 (13.3%)	0 (0%)
Group B	41 (91.1%)	4 (8.9%)	0 (0%)	0 (0%)
p	0.569	0.705	0.034	-

Values are expressed as n (%). Percents are shown in comparison with the whole population.



Figure 2. A patient before and after treatment

therapy are the most effective and safe topical treatment methods for vitiligo.^[34,35]

In this trial, we aimed to add some topical agent (5FU) to the previously known corticosteroid agents to reduce the time interval of the response and accelerate the response rate. Although as a chemotherapeutic and immunomodulatory drug, 5FU has been previously used for local therapy in vitiligo treatment, the results were unsatisfactory.^[21,36]

As we showed in our study, topical clobetasol and its combination with 5FU were both quite effective in healing vitiligo patches. Similar findings were reported by meta-analyses on corticosteroids.^[34,35]

We found clobetasol with every other day frequency to be quite effective in our 3-month trial. Due to the potential danger of topical potent corticosteroids in induction of skin atrophy, the every other day protocol may be a logical way to prevent side effects and obtain quite satisfactory results.

In our trial, the response to treatment with clobetasol plus 5FU (the right side) was significantly better than clobetasol alone (left side). Therefore, 5FU accelerated the improvement rate. In addition, good patient tolerance on the right side accelerated patients' response and thus increased the response rate. This may rein-

force patients to continue their therapy, increase their satisfaction, have a good impact on patients' social and familial relationships, and finally promote their quality of life.

In our patients, the pattern of repigmentation was diffuse rather than perifollicular which might have been caused by the prolonged drug usage. It seems that the primarily perifollicular repigmentations merged together and made uniform patches and the perifollicular pigmentation could not hence be detected.

Abd-El Samad Ibraheim evaluated the efficacy of intradermal injection of 5FU in 45 patients with localized UV-therapy resistant vitiligo patches. By adding weekly intradermal injections of 5FU (50 mg/ml) to 2 topical UV therapies in 3 groups of patients, excellent, good, and moderate responses were observed in 66.7% (75-100% repigmentation), 20% (51-75% repigmentation), and 4.4% (26-50% repigmentation) of the patients, respectively. Although side effects such as pain, burning sensation, hyperpigmentation at the border of the lesion were reported, similar to our study, no case was eliminated due to side effects. However, the pattern of repigmentation was more follicular mainly at sites of injection (66.6%) rather than diffuse (22.2%).^[27]

In our study, 3 months of clobetasol plus 5FU resulted in pigmentation in 88.8% of the patients with moderate, good, and excellent responses in 33.3%, 22.2%,

and 33.3% of patients. Therefore, over 50% of our patients achieved good to excellent results which is quite satisfactory both for the patient and the physician. In our trial, the pattern of pigmentation was more diffuse (88.8%) rather than follicular (20%). This type of repigmentation is more acceptable in the cosmetic view.

Side effects of clobetasol plus 5FU were mild and transient and we had surface erosions only in 3 patients. Perhaps, the difference between our results and Abd-El Samad Ibraheim's is due to different ways of administering 5FU (topical vs. injections). Moreover, adding topical corticosteroid with its anti-inflammatory effects may reduce the irritation. It seems that the 5FU could be safely tolerated by the vitiligo patients. The more visible side effects with 5FU administration which are routinely seen in patients with actinic keratosis seems to be due to the lesional characteristics and the pathology of the underlying skin which is more vulnerable to irritating effects of 5FU.

Sethi et al. evaluated the therapeutic efficacy of adding 3 protocols to dermabrasion. They added topical 5FU 5%, a soframycin tulle dressing, or topical placentex gel dressing on a previously dermabraded vitiligo lesion. The response rate in 5FU group was 56.6% (repigmentation > 50%) at 4 months and 73.3% (repigmentation > 50%) at 6 months. Therefore, dermabrasion combined with 5FU was suggested as the most efficacious among the 3 treatment modalities.^[29]

On the other hand, as we used topical drugs, the simplified method of drug administration may reinforce patients' compliance.

The therapeutic effect of 5FU on vitiligo may originate from several mechanisms. The drug may induce a type of epidermal injury which can break the integrity of the epidermis and stimulate the amelanotic (inactive) melanocytes (present at the outer root sheath of the lower portion of the hair follicle) to proliferate and migrate afterward to the top and start actively to synthesize melanin at the infundibulum. They would then migrate upward until they reach the surface of the skin. This appears clinically as perifollicular pigmentation which gradually enlarges to cover the whole depigmented area. Therefore, depigmented hair in the vitiliginous patches denotes bad prognosis because the pigmented hair acts as melanocytes reservoir for repigmentation.

In another suggested mechanism, 5FU produces the colonization of melanocytes in the vitiliginous epidermis by stimulating the division of epidermal melanocytes

and reinforcing their migration toward the affected areas after epithelialization of the epidermis. Alternatively, the melanocytes responsible for repigmentation in vitiligo may be derived from the hair follicles.

At the cellular level, 5FU competes with deoxyuridine and its derivatives for the substituting sites of the enzyme thymidylate synthase. This enzyme is a potent inhibitor of a variety of cellular functions and could destruct most living cells including pigment cells. Hence, 5FU does not only stimulate the growth of pigment cells, but also protects them from the damages that may be induced by several inhibitory agents.^[31,36,37]

Other mentioned mechanisms for 5FU action are increased level of melanocyte-stimulating hormone, direct stimulation of melanocytes, increased number of melanosomes in the keratinocytes, and activation of melanocytes. However, hyperpigmentation is a known side effect of 5FU and is observed during the treatment of skin tumors and psoriasis.^[28,29,38,39]

Considering the existing abnormalities in immunoregulation in the patches of vitiligo, the immunomodulatory effects of 5FU can act as further mechanisms in treating vitiligo.

As we showed in our study, no side effects were added by combining clobetasol with 5FU. The drug can thus be used conveniently by the patient.

Conclusion

This double-blind clinical trial outlined the more acceptable efficacy of combining 5FU with corticosteroid than corticosteroid alone which is the routine treatment of vitiligo.

As vitiligo may have a deep disturbing effect on quality of life in both patients and their relatives, examining new modalities in the treatment approach could be very helpful.

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