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Efficacy of Intradermal Injection of 5-Flurouracil in the Treatment of Vitiligo

[1]Sahbaa Mohamed Abdelshafy, [1]Samia Ali Ibrahim, [1] Ahmed Said Abdelshafy[1]

[1]Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University.

Corresponding Author Email: drsahbaa@gmail

Abstract

Background: Vitiligo is a chronic skin disorder characterized by patchy loss of skin color and affects approximately 0.5% to 2% of the world's population. 5-Flurouracil (5-FU) was tried in treatment of vitiligo in combination with NB-UVB, but was preceded by either dermabrasion or laser ablation of the vitiligo area to ensure more penetration of 5-FU into the skin. The intralesional 5-FU solution injection is an effective treatment of localized vitiligo and its effects were maintained for 6 months.The aim of the work was to assess the efficacy and safety of intradermal injection of 5-Flurouracil in the treatment of vitiligo.Patients and methods: A total number of 14vitiligopatients were included in the study. They were collected from Out-patient clinic of Dermatology, Venereology and Andrology department, Faculty of Medicine, Zagazig University. All the patients were subjected to complete history taking, complete general examination and clinical examination of vitiligo area. Then, intradermal injectionof 5-Flurouracil every 2 weeks for 3 months was done. Any complications were recorded andpatients were photographed before and after treatment to assess the clinical repigmentations.Results:Efficacy of the treatment was 78.6% but the efficacy of treatment of acral type was the lowest among vitiligo cases.Conclusion:Intradermal injection of 5FU is safe and effective inthe treatment of vitiligo.

Key words:vitilgo, 5-Flurouracil, depigmentation, repigmentation

Introduction

Vitiligo, a depigmenting skin disorder, is characterized by the selective loss of melanocytes, which in turn leads to pigment dilution in the affected areas of the skin. The characteristic lesion is a totally amelanotic, nonscaly, chalky-white macule with distinct margins [1]. An international consensus classified vitiligo into two major forms: nonsegmental vitiligo (NSV) and segmental vitiligo (SV) [2]. Vitiligo is the most common depigmenting skin disorder, with an estimated prevalence of 0.5–2% of the population in both adults and children worldwide [3]. Considerable progress has been made in our understanding of the pathogenesis of vitiligo. It is a multifactorial disorder characterized by the loss of functional melanocytes. Multiple mechanisms have been

proposed for melanocyte destruction in vitiligo. These include genetic, autoimmune responses, oxidative stress, generation of inflammatory mediators and melanocyte detachment mechanisms [4].The skin plays an important role in our interaction with the world, and visible skin disorders can limit healthy psychosocial development owing to the stigma these disorders create [5]. The treatment of vitiligo is still one of the most difficult dermatological challenges. These treatments include phototherapy, topical and systemic immunosuppressants, and surgical techniques, which together may help in halting the disease, stabilizing depigmented lesions and stimulating repigmentation [4].

Fluorouracil (5-FU) has an antimitotic activity with selective cytotoxicity against rapidly proliferating keratinocytes which has been used in the treatment of nonmelanoma skin cancers. One of its side effects is hyperpigmentation [6]. It has been postulated that these hyperpigmentationsarepostinflammatoryhyperpigmentations on sites submitted to repeated friction [7].

In the presence of low concentrations of 5-FU, keratinocytes are selectively destroyed within three weeks, while melanocytes continue to multiply and to form pigment [8]. Until now, it was difficult to understand why a topical drug, such as 5-FU, well known for its antimitotic activity, could improve the proliferation and migration of melanocytes. Successively, a direct overstimulation of melanocyte proliferation (unproven in melanocytes cultures), an inhibition of agents or cells able to destroy pigment cells, and finally an immunomodulation stabilizing the vitiligo disease [9]. The aim of our study was to assess the efficacy and safety of intradermal injection of 5-Flurouracil in the treatment of vitiligo.

Patients and methods

A total number of 14 vitiligo patients were included in the study. They were collected from Out-patient clinic of Dermatology, Venereology and Andrology department, Faculty of Medicine, Zagazig University in the period from December 2019 to January 2021. Inclusion criteria included: Newly diagnosed patients with localized Vitiligo of both sexes who didn't receive other treatment modalities for at least three months. Exclusion criteria included: pregnancy, lactation, renal or hepatic failure, present Skin cancer or history of skin cancer, immunosuppressed patients,hypersensitivity to 5-flurouracil and bone marrow depression.All patients were subjected to the following:complete history taking and complete general examination.Clinical examination of vitiligo areaand photo documentation using a digital camera in 350 megapixels were done. After that, intradermal injectionof 5-Flurouracil (Utoral vial 50 mg/ml), 0.01-0.02 ml per injection with 1 cm apart, using insulin syringe 26 gauge every 2 weeks for 3 months.

Complications such as erythema, pain, ulceration, burning sensation, ecchymosis, infection, postinflammatory hyperpigmentation, and any allergic manifestations were recorded. Patients were photographed before and after treatment and assessment of

clinical repigmentations were made according to a 5-grade scale ranging from G0 to G4in which achieving at least 75% repigmentation of vitiliginous lesions was known as an 'excellent' result, or a score of 4 (out of 4). Repigmentation of 51–75% was a 'good' response, or a score of 3, and 25–50% repigmentation was a moderate response, or a score of 2 [10].The patients were followed-up monthly for 3 months after the end of the treatment sessions to detect any recurrence, complications or worsening of the lesions.

Ethical Considerations

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Written informed consents were obtained from the study participants. Approval by IRB research committee of Zagazig Faculty of Medicine was also included.

Statistical Analysis

The data were coded, entered and processed on computer using Statistical package for social science (SPSS) (version 18).The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were used as descriptive statistics.

Results

Demographic characteristics of patients are shown in table (1). Mean age of the study populations was (38.07 ± 10.18). The percentage of females was more than males. 21.4% of patients didn't receive any previous treatment while 78.6% received previous therapy. Regarding sites of vitiligo lesions, 21.4% had facial lesions, 42.9% had acral lesions and 35.7% had body lesions as can be seen in table (2).

Table (1): Demographic characteristics of vitiligo patients

			Vitiligo patients
Age	**Range**		23-56
	Mean ± SD		38.07 ± 10.18
Sex	**Female**	**No.**	12
		%	85.7%
	Male	**No.**	2
		%	14.3%
Family history	**negative**	**No.**	9
		%	64.3%
	positive	**No.**	5
		%	35.7%
Duration	**<48 months**	**No.**	6
		%	42.9%
	> 48	**No.**	8

	months	%	57.1%
Previous treatment	not received	No.	3
		%	21.4%
	received	No.	11
		%	78.6%

Table (2): Distribution (facial, Acral and Body) of vitiligo lesion.

			Vitiligo patients
Site (facial)	No	No.	11
		%	78.6%
	Yes	No.	3
		%	21.4%
Site (Acral)	No	No.	8
		%	57.1%
	Yes	No.	6
		%	42.9%
Site (Body)	No	No.	9
		%	64.3%
	Yes	No.	5
		%	35.7%

Table (3): Side effects of the treatment (pain, itching, dryness, hyperpigmentation and erythema).

Side Effects			Vitiligo patients
Pain	No	No.	0
		%	0%
	Yes	No.	14
		%	100.0%
Itching	No	No.	13
		%	92.9%
	Yes	No.	1
		%	7.1%
Dryness	No	No.	14
		%	100.0%
	Yes	No.	0
		%	.0%
Hyperpigmentation	No	No.	5
		%	35.7%
	Yes	No.	9

		%	64.3%
Erythema	No	No.	13
		%	92.9%
	Yes	No.	1
		%	7.1%

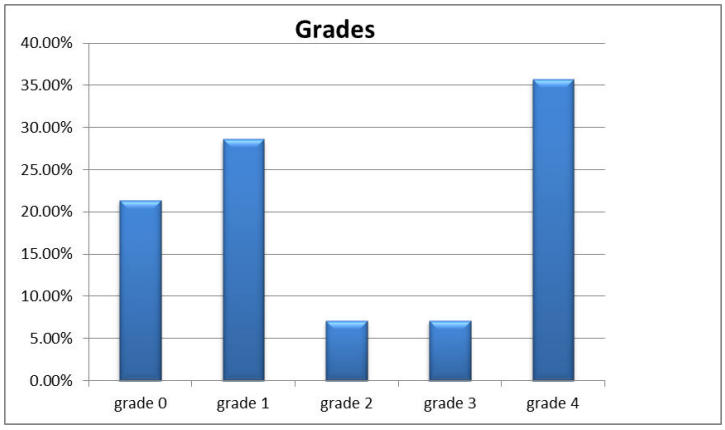

Figure (1): Clinical response in grades in the study group.

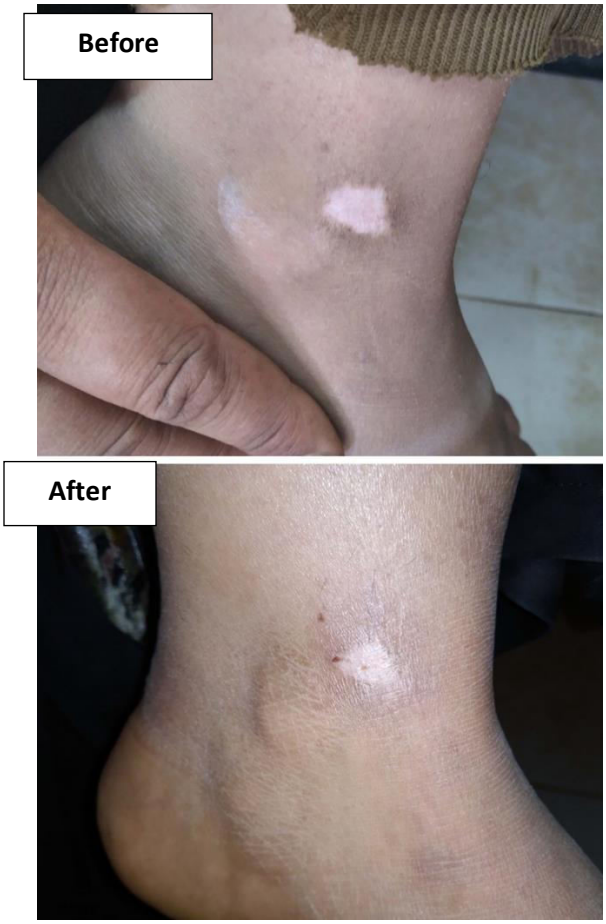

Figure (2): vitiligo lesions before and after treatment with 5 FU (grade 2).

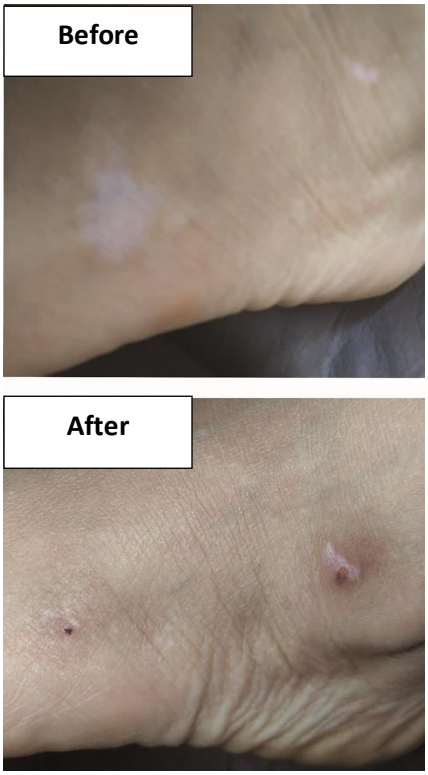

Figure (3): vitiligo lesions before and after treatment with 5 FU (grade 4).

Regarding the efficacy of treatment, the percentage was 78.6% among those patients. The Efficacy of the treatment was calculated as follow: any repigmentation of the vitiligo lesions starting from grade 1 to grade 4 was considered an effective treatment.Figure (1)demonstrates that the percentage of patients with grade 0 was (21.4%), grade 1 was (28.6%), grade 2 was (7.1%), grade 3 was (7.1%) and grade 4 was (35.7%). Figure (2) demonstrates the lesions before and after the treatment in grade (2) and Figure (3) shows the lesions before and after the treatment in grade (4).The efficacy of the treatment of facial lesions was 100%, 66.4% for acral lesions and80% for body lesions. As can be observed in table (3), the main side effects were pain and hyperpigmentation with percentage100.0% and 64.3% respectively while erythema and itching occurred at equal percentages (7.1%).

Discussion

Numerous therapeutic modalities have been recommended for vitiligo such as phototherapy, topical and systemic corticosteroids, calcineurin inhibitors, vitamin D3 analogue derivatives, 5-Flurouracil, laser therapy, and surgical techniques. However, there is no treatment ensures complete cure of vitiligo. Therefore, combination therapy is frequently recommended [11].

The present work aimed to assess the efficacy of intradermal injection of 5-Fluorouracil in the treatment of vitiligo.Our study showed female predominance among the studied groups.This result is in agreement withZahra et al., (2020) who made interventional prospective study that was conducted from July 2018 to June 2019 with total of 60 vitiligo patients and found female predominance in their study (62%) [12]. These results were also consistent with the results obtained by George et al. (2017) [13]. This probably reflects the increased social stigma of vitiligo in female patients, and thus early treatment-seeking behavior. Whereas, Lee et al., (2015) revealed males and females are equally affected, although women and girls often seek consultation more frequently, possibly due to the greater negative social impact than for men and boys [14].In the current study, Efficacy of treatment was 78.6%.Zohdy and Hussein, (2018) demonstrated that in localized nonsegmental vitiligo (NSV), intradermal 5-FU showed better overall improvement compared with intradermal triamcinolone. Its effects were maintained for 6 months, whereas that of triamcinolone stopped at 1 month after the last injection [15]. These findings were comparable with the result of study made by Abd El-Samad and Shaaban (2012) who aimed to evaluate the efficacy and safety of intradermal injection of 5-flurouracil (5-FU) as a treatment option for vitiligo.

Their study included 60 vitiligo patients with overall symmetrical lesions affecting less than 30% of body surface area. They found that the efficacy of the treatment was 78% among 5FU injection treatment group [16].There is no consensus on the standard measure of treatment efficacy in vitiligo. Excellent repigmentation rates varied from 12.5% to 61% of patches in various studies [10]. Khater et al., (2020) found that43.8% of patients treated with 5-FU showed good to excellent response (repigmentation>50%) [17].

This study showed that, Treatment of acral type of vitiligo had lower treatment response among vitiligo cases that is similar to the study conducted by Dillon et al., (2017) whofound that the acral type of vitiligo had lower treatment response [18].Noriega et al., (2017) revealed that, the mechanism by which 5-FU induces the repigmentation of vitiligo is still a matter of debate which may be due to the overstimulation of follicular melanocytes, inhibition of agents or cells able to destroy melanocytes, and/or selective keratinocytes destruction by 5-FU while melanocytes continue to multiply and to form pigment. The hydrophilic drugs such as 5-FU need to be delivered into epidermis avoiding the stratum corneum barrier [19].Our results can be applied not only for localized areas of vitiligo but also suitable for relatively large areas of vitiligo unlike minigraft or melanocytes transplantation.In this work, pain was present because of the injection but it did not interfere with the completion of treatment.This was in agreement with that reported by Abd El-Samad and Shaaban, (2012) who reported that the side effects were very minimal including pain during injections that disappeared within few minutes and did not interfere with the patient compliance [16].

Conclusion: Intradermal injection of 5FU is safe and effective in the treatment of vitiligo.

Declaration of interest: The authors report no conflicts of interest

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References

1) Ezzedine K, Eleftheriadou V, Whitton M et al. (2015): Vitiligo. Lancet ;386(9988):74-84
2) Ezzedine K, Diallo A, Léauté-Labrèze C, et al. (2012): Halo nevi association in nonsegmental vitiligo affects age at onset and depigmentation pattern. Arch Dermatol. 148(4):497–502.
3) Krüger C, Schallreuter KU. (2012): A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol. 51(10):1206–12.
4) Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE; (2017): Vitiligo Working Group. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol. 77(1):1–13.
5) Roman J. (2016): Beauty That Is More Than Skin Deep. JAMA Dermatol. 152(5):562–3.
6) Jha AK, Sonthalia S. (2019): 5-Fluorouracil as an adjuvant therapy along with microneedling in vitiligo. J Am Acad Dermatol. 80(4):e75–6.
7) Van Tienhoven G. and J. W. Wilmink. (2011): "A woman with palmar and plantar hyperpigmentation," NederlandsTijdschriftvoorGeneeskunde, vol. 155, no. 45, p. 4100.
8) Tsuji T. and M. A. Karasek, (1986): "Differential effects of 5-fluorouracil on human skin melanocytes and malignant melanoma cells in vitro," Acta Dermato-Venereologica, vol. 66, no. 6, pp. 474–478.
9) Anbar TS, Westerhof W, Abdel-Rahman AT et al. (2008): Effect of one session of ER:YAG laser ablation plus topical 5Fluorouracil on the outcome of short-term NB-UVB phototherapy in the treatment of non-segmental vitiligo: A left-right comparative study. PhotodermatologyPhotoimmunology and Photomedicine, 24(6), 322–329 .
10) Batool S, Malik LM, Jahangir M. (2015): Efficacy of narrowband ultraviolet B phototherapy with needling in patients of vitiligo. JPAD. 25:177-182.
11) Neinaa YME, Lotfy SS, Ghaly NR, et al. (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.

12) Zahra FT, Adil M, Amin SS, et al. (2020): Efficacy of Topical 5% 5-Fluorouracil with Needling versus 5% 5-Fluorouracil Alone in Stable Vitiligo: A Randomized Controlled Study. *J CutanAesthet Surg*. 13(3):197-203.
13) George M, Mallikarjun M, Manjunath P, et al. (2017): Efficacy of laser dermabrasion followed by topical 5-fluorouracil in the treatment of stable vitiligo. Int J Health Sci Res. 7:144–7.
14) Lee H, Lee MH, Lee DY, et al. (2015): Prevalence of vitiligo and associated comorbidities in Korea. Yonsei Med J. 56(3):719–25.
15) Zohdy HAEW and Hussein MS (2018): Intradermal injection of Fluorouracil versus triamcinolone in Localizes vitiligo treatment. Journal of Cosmetic Dermatology ;00:1–5.
16) Abd El-Samad Z and Shaaban D (2012):Treatment of localized non-segmental vitiligo with intradermal 5-flurouracil injection combined with narrow-band ultraviolet B: A preliminary study.Journal of Dermatological Treatment, 23:6, 443-448
17) Khater, M., Nasr, M., Salah, S., et al. (2020). Clinical evaluation of the efficacy of trichloroacetic acid 70% after micro-needling vs intradermal injection of 5-fluorouracil in the treatment of non-segmental vitiligo; a prospective comparative study. Dermatologic Therapy. e13532.
18) Dillon, A. B., Sideris, A., Hadi, A., et al. (2017). Advances in Vitiligo: An Update on Medical and Surgical Treatments. The Journal of clinical and aesthetic dermatology, 10(1), 15–28.
19) Noriega LF, Noriega AF, Contin LA. (2017): A new important tool in the treatment of the idiopathic guttate hypomelanosis: Report of two cases. J Med OnclTher. 2: 3.