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Efficacy of intra lesional injection of 5-flourouracil on keloid scar: A prospective open clinical trial

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Abstract

Background and objectives: The management of keloids stayed unsatisfactory. Intralesional 5-fluorouracil has not been broadly and intensively studied as a monotherapy in the treatment of keloids worldwide. So, the aim of this study was to evaluate the efficacy and safety of intralesional injection of 5-flourouracil in patients with keloids.

Methods: In this prospective clinical trial study, a total of 20 patients aged >18 years at Shahid Jabar Dermatological Teaching Center, Sulaimaniyah, Iraq, from January 2022 to August 2022 were enrolled. Patients were treated at 1-week interval with intralesional injection of 5-flurouracil (50 mg/mL) at maximum of 6 sessions. Average injection volume was 0.2 mL/cm^2. All patients were followed up for 6 months.

Results: Most of the patients were aged <50 years (90%) with no family history of keloid (75%). Additionally, 45% of patients had keloid in the trunk region with a size of ≤10 cm^2 (65%). Most patients (80%) had the disease for ≤5 years that caused by inflammation (55%), especially skin type IV (65%). After 6 sessions of treatment, 70% of patients showed moderate improvement, while 30% of patients showed minimum improvement. The main adverse effects after 6 sessions of treatment were hyperpigmentation in 3 patients, bullae in 2 patients, and tissue sloughing only in 1 patient. A significant correlation was found between the patient's response and age/keloid location. Moreover, mean Redness, Elevation, Hardness, Itching, and Tenderness score after treatment was significantly lower than before treatment ($p<0.001$).

Conclusions: Our results concluded that 5-flurouracil is a safe and effective therapy for the treatment of keloids.

Keywords: Antineoplastic agent, Monotherapy, Prospective-clinical trial study, Skin disorder

Introduction

Keloids are benign hyperproliferative skin diseases in which the skin grows outside the initial lesion that is not regress spontaneously and tends to recur after excision.[1] Generally, keloids have been thought to be the outcome of aberrant wound healing,

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acne formation or chickenpox infection that results in an excessive dermal fibroblast activity which characterized by hyalinized collagen bundles. The highest incidence of keloids was found in Blacks and dark-skinned individuals.[2]

Although the precise origin of this condition is unknown, however; genetic and environmental factors are certainly involved.[3] Additionally, the cytokine transforming growth factor-b (TGF-b) has been linked to the pathophysiology of keloids, and the interaction between elevated TGF-b levels and the aberrant proliferative scar fibroblast response to this cytokine may lead to the development of keloid lesions.[4] The association with hormones has also been found with increased susceptibility in acromegaly, increased growth during pregnancy, puberty and hyperthyroidism.[5]

Keloids can occur anywhere on the body, but typically develop on areas of the body that are highly mobile and under a lot of tension, such as the shoulders, neck, and presternum, however, lesions on the sternum, earlobes, and cheeks can also be found.[6] In general, keloid less commonly occurs to the eyelids, cornea, palms, mucous membranes, genitalia, and soles.[7] Keloids may lead to significant morbidity, pruritus, pain, restriction of motion,[8] or cosmetic disfigurement in affected patients.[9]

There is uncertainty about the best course of treatment for keloids, which may involve surgical excision, cryotherapy, laser therapy, low-dose radiation, silicone sheeting, topical retinoid, and intralesional injections of triamcinolone acetonide, 5-fluorouracil (5-FU), and bleomycin.[10, 11] Thus, new therapeutic choices have arisen as a possible option to increase treatment efficacy without side effects, one of which is 5-FU.[12] 5-fluorouracil is a fluorinated pyrimidine antimetabolite that prevents the irreversible conversion of uridine to thymidine by thymidine synthase, prevents the formation of deoxyribonucleic acids, rapidly growing cells, like fibroblasts, are blocked and scar degeneration is accelerated without the structural components of biosynthesis.[13, 14] It may substantially improve the appearance of proliferative scars and reduce the chance of recurrence.[15] Therefore, we conducted this prospective open clinical trial study to assess therapeutic efficacy and usefulness of 5-FU in the treatment of keloid of any duration or size.

Patients and methods

This prospective open clinical trial study was conducted on 20 patients with keloid lesions at Shahid Jabar Dermatological Teaching Center, Sulaimaniyah, Kurdistan Region, Iraq, from January 2022 to August 2022. The study proposal was approved by the Kurdistan Higher Council of Medical Specialties (KHCMS), Sulaimaniyah, Iraq (No. 59-11-01-2022-KHCMS). On the other hand, a written informed consent was obtained from each patient and their confidentiality/anonymously were preserved. The patients also felt free to quit from the study any time they need without reason. A validated questionnaire was prepared to collect patient's sociodemographic data, including age, gender, and family history of keloids. Also, patient's clinical characteristics such as the location/size of the keloids, duration of the disease, and skin type were also obtained together with main causes of the disease (such as trauma, burn, infection, or any inflammatory skin disorder), any prior medication for keloids, and evidence of any systemic disease were obtained.

Patients aged >18 years that not received any medications for keloids in the last 2 months were involved in this study regardless of gender. Pregnant and lactating women, immunosuppressed patients, and those had liver and renal diseases, acute/chronic infections were excepted from the study. Examination was done for each patient regarding number, size, and

site of the keloid. Any prior treatment was discontinued for at least 2 months before starting intralesional 5-FU. Regarding investigations, all patients had full blood cell count along with renal and liver function tests checked before treatment as a baseline, and once after treatment were commenced.

Before starting the therapy, 70% ethanol was used as a topical antiseptic agent to clean the lesion. Then, 5-FU (Kocak Company, Turkey) intralesional injection (50 mg/mL) in the amount of 0.2 mL/cm² using disposable insulin syringe (27-gauge needle) directly injected into the substance of keloid and the solution pushed with adequate pressure till minimal blanching was seen. Maximum of 6 sessions with 1-week interval was done, and the patients were followed up for 6 months. REHIT criteria (Redness, Elevation, Hardness, Itching, and Tenderness) was used to evaluate patient's response.[16] Then, the responses were graded as no, minimal, moderate (improvement more than minimal and less than complete), and complete responses (change of the score into 0 in all criteria) (Table 1). Consequently, any side effect appeared in treated patients has been recorded and photographs has been captured (before and after treatments). Finally, the data were analyzed using Statistical Package for the Social Sciences (SPSS, version 26, Chicago, USA). The Paired sample t-test was used to compare the mean scores before and after treatments. Chi-Square test was used for testing the categorical variables. Frequencies and percentages also were calculated. P-values of ≤0.05 considered as significant difference, while p-values of <0.001 considered as highly significant difference[16].

Table (1): REHIT criteria (Redness, Elevation, Hardness, Itching, and Tenderness).

Criteria	Score
A. Redness	3: Severe redness associated with telangiectasia 2: Redness disappears with pressure. 1: No redness but a dark appearance. 0: Normal skin color.
B. Elevation	3: More than 8 mm in height above the surrounded skin. 2: 4-8 mm. 1: 1-4 mm. 0: Flat or depressed scar.
C. Hardness	3: Very hard, like a cartilage. 2: Rubbery hard. 1: Partially soft. 0: Soft.
D. Itching	3: Severe itching sensation, or constantly itchy with signs of scratching. 2: Occasional itchy sensation, moderate and tolerable. 1: Sometimes itchy. 0: No itchy sensation.

E. Tenderness and pain	3. Severe irritable pain 2: Moderately irritable pain. 1: Sometimes painful. 0: Without pain.

Minimal response includes change of one score in no more than 3 criteria or change of one score in no more than 2 criteria provided that one or more criterion was ranking 0 score before embarking upon our treatment. Moderate response means improvement more than minimal and less than complete.

Results

The mean±SD age of patients was 33.75±13.66 years. Most of them were aged <50 years (90%), male gender (60%) with no family history of keloid (75%), Table (2).

Table (2): Sociodemographic characteristics of the enrolled patients.

Variable	Item	No.	%
Age (Year)	<30	9.0	45
	31-50	9.0	45
	>50	2.0	10
Gender	Male	12	60
	Female	8.0	40
Family history of keloid	Negative	15	75
	Positive	5.0	25

In the current study, the most common location of the keloid was in the trunk area (45%), and 65% of patients had a keloid size of ≤10 cm^2. Regarding the keloid duration, 80% of the patients had the disease for ≤5 years and the main cause of the disease was inflammation (55%), while the most predominant skin type was type IV (65%), Table (3).

From the total of 20 patients, 70% had moderate response as shown in Figure (1), while 30% had minimum response based on Sharquie et al., 2003 [17], Table (4).

Table (3): Clinical characteristics of the keloids in the studied patients.

Variable	Item	No.	%
Location	Ear	4.0	20
	Trunk	9.0	45
	Upper extremity	7.0	35
Size (cm^2)	≤10	13	65
	11-19	3.0	15
	≥20	4.0	20
Duration (Year)	≤5.0	16	80
	>5.0	4.0	20
Cause	Burn	3.0	15
	Inflammation	11	55
	Trauma	6.0	30
Skin type	Type III	7.0	35
	Type IV	13	65

Table (4): Response of the patients to 5-FU treatment.

Patient's response	No.	%
No	0.0	0.0
Minimum	6	30
Moderate	14	70
Complete	0.0	0.0
Total	20	100

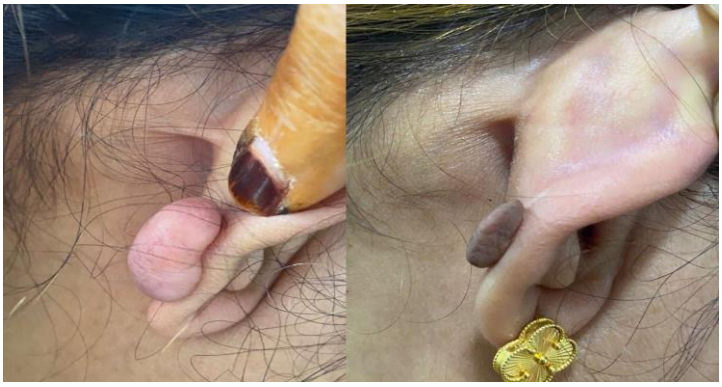

Figure (1): Comparison of the keloid size in the patient before (left) and after (right) 5-FU treatments.

In the current study, significant differences were observed between the patient's response (minimum/moderate) in relation to keloid location (p=0.017) and their ages (p=0.03) in which the patients who aged 31-50 years had better response than other age groups. While no significant differences between the patient's response in regards to gender (p=0.55) and size of keloids (p=0.96) were seen, Table (5).

Table (5): The patient's response in regard to the age, gender, keloid location and size.

Variable	Item	Response			p value
		Minimum (No., %)	Moderate (No., %)	Total (No., %)	
Age (Year)	<30	5.0 (83.3)	4.0 (28.6)	9.0 (45)	0.03*
	31-50	0.0 (0.0)	9.0 (64.30	9.0 (45)	
	>50	1.0 (16.7)	1.0 (7.1)	2.0 (10)	
Gender	Male	3.0 (50)	9.0 (64.3)	9.0 (60)	0.55
	Female	3.0 (50)	5.0 (35.7)	9.0 (40)	
Keloid location	Ear	4.0 (50)	0.0 (0.0)	4.0 (20)	0.017 *
	Trunk	3.0 (37.5)	6.0 (50)	9.0 (45)	
	Upper extremity	1.0 (12.5)	6.0 (50)	7.0 (35)	
Keloid size (cm^2)	≤10	4.0 (66.7)	9.0 (64.3)	13 (65)	0.96
	11-19	1.0 (16.7)	2.0 (14.3)	3.0 (15)	
	≥20	1.0 (16.7)	3.0 (21.4)	4.0 (20)	
Total		6.0 (100)	14 (100)	20 (100)	

*: Significant difference

Mean REHIT score after 6-sessions of treatment was significantly lower than before treatment with intralesional injection of 5-FU ($p<0.001$), Table (6).

Table (6): Distribution of mean REHIT score of the patients before and after treatments.

Variable	Mean±SD	p value
Before treatment	11.05±1.5	<0.001**
After treatment	3.1±0.85	

**: Highly significant difference

At the time of injection, all patients had moderate pain, but only 2 patients reported itching. Post-inflammatory hyperpigmentation (PIH) found in 3 patients (15%), bullae in 2 patients (10%) and sloughing in 1 patient (5%).

Discussion

Generally, the keloid treatment is challenging and sometimes the outcomes are not promising. However, clinical trials and studies are continuously conducted to overcome this skin lesion worldwide using various techniques, agents, and medications. To the best of our knowledge, this is the first study in our country using 5-FU chemotherapy for the keloid treatment.

In this study, the keloid lesions most predominantly found in males aged <50 years without family history of the disease. These outcomes are consistent with Prabhu et al. who found >90 of males with keloids were aged <55 years.[18] The mean age of the patients was 33.75±13.66 years, which is consistent to that found by Saha and Mukhopadhyay, who reported their patient's mean age of 34.7 ± 11.0124 years.[19] However, Srivastava et al. found the equal gender distribution of the patients with mean age of 27.55±8.54 years.[20] On contrary, Sun et al. in a nation-wide population based study in Taiwan found a gender prediction of keloids to females aged 30.8±15.4 years with highest incidence among those aged 20-29 years.[21] Also, Noishiki et al. observed that females were twice as prevalent as males at nearly all onset ages to get keloid lesions and they suggest that female sex may promote early keloid development due to physiological reasons.[22] Moreover, Liu et al. found that 65.3% of patients with keloid were females with mean age of 34.37±14.92 years.[23]

Concerning the family history of keloid, most of our patients showed negative correlations which is not agreed with that found by Lu et al. who determined that a greater severity of keloids was in the positive history family group with significant difference.[24] Also, Kouotou et al. reported that existence of a family history of keloids was significantly associated with presence of keloids.[25] However, our findings, agreed with that found by Shaheen et al. 2016 who mentioned that only 19.3% of patients had family history of keloids,[26] as well as Belie et al. mentioned that only 25% of patients had positive family history of keloid.[27]

Regarding the main cause of keloid in our patients, inflammation (55%), followed by trauma (30%), and burn (15%) which agrees with that found by Srivastava et al. who indicated that most patients (55%) had infection, followed by trauma (25%).[20] Moreover, our studied patients presented with keloid lesions on their trunk region that commonly sized ≤ 10 cm^2. These results are agreed with that found by Prabhu et al. who found 44.8% of patients had a keloid lesion on their shoulder area,[18] while it is not agreed with that found by Srivastava et al. who explored that most lesions were found in presternal region (60%), followed by extremities (20%), and then trunk/face (10% each).[20] However,

Khalifa and Muhsin, found that BCG keloid was observed in females only which downward gravitational extension in 43% of patients.[2] Similarly, Sun et al. reported that females with leiomyoma had a greater risk of keloids.[21]

Regarding the duration of having keloid lesion in studied patients, most of them (80%) developed the lesion in <5 years, while Prabhu et al. reported that most of patients (51.7%) developed the lesions between 1-3 years.[18] On the other hand, Nanda et al. reported that the duration of keloid history in patients was from 6 months to 15 years,[28] while Bijlard et al. found keloid duration to be 1-40 years in studied patients,[29] and Liu et al. found the mean duration of keloid was 12.33±9.68.[23]

Also, we used intralesional 5-FU monotherapy for 6 sessions with 1-week interval which is similar to that reported by Sharma et al. that used 5-FU for ≤12 weeks,[30] and also to that conducted by Nanda et al. 2004 who used 5-FU for 12 weeks with 1-week interval.[28] Majority of our patients (70%) had moderate response to intralesional 5-FU monotherapy. In this regard, Sharma et al. who reported good to excellent response in 72% of patients treated with intralesional 5-FU.[8] Whereas Kontochristopoulos et al. who reported that 82% of the patients showed 50% improvement after 5-FU injection in to the lesions.[10]

On the other hand, only 30% of our treated patients showed side-effects after treatment, including hyperpigmentation, bullae, and sloughing. Whereas drastically improved of lesions such as pruritus, pain, tenderness, restriction of movements was found in another study.[8] In this regards, Saha and Mukhopadhyay found 6% of the patients presented soon after the first 2-3 sessions with superficial ulcerations at the injection site accompanied by mild discomfort and discharge.[19] Simultaneously, hyperpigmentation, sloughing, and pain were recorded as the main side effects after using intralesional 5-FU by Kontochristopoulos et al.[10] However, only skin atrophy was recorded in 8% of patients who received intralesional 5-FU in a study conducted by Hietanen et al.[31]

Consequently, in the current study, age and keloid location were substantially correlated to the patient's response to the treatment, while gender and size of keloids did not. Younger aged patients responded better to the treatment than older patients, but the treatment outcomes were not affected by gender or even keloid size.

In the present study, the mean REHIT score after treatment was significantly lower than before treatment. This finding agrees with that found by Alexandrescu et al. who demonstrated that intralesional 5-FU monotherapy was more efficacious than the other modalities, including 5-FU/kenalog, 5-FU/verapamil, enalapril, verapamil, and laser in reducing clinical signs of keloids.[32] Same findings were observed by Srivastava et al.[20]

Conclusions

We concluded that keloids were more frequently reported in middle aged peoples (<50 years) without family history of the disease. Additionally, trunk region is the common area to be affected. Also, inflammation was the main cause of the disease in patients that had the disease for ≤5 years, especially those with skin type IV. Collectively, we found that intralesional 5-FU monotherapy might be effective in the keloids treatment as 70% of treated patients with 5-FU had moderate response and 30% had mild response, while none of the patient achieved complete response.

Conflict of interest

The authors declare that there is no conflict of interest to this study.

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