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Original Article

Comparison of efficacy of intralesional 5-fluorouracil plus triamcinolone acetonide versus intralesional triamcinolone acetonide in the treatment of keloids

Farah Saleem*, Zahida Rani, Bushra Bashir*, Faria Altaf*, Khawar Khurshid*, Sabrina Suhail Pal***

* Dermatology Department, Unit II, King Edward Medical University, Mayo Hospital, Lahore
** Dermatology Department, Khawaja Safdar Medical College, Sialkot
*** Dermatology Department, Gujranwala Medical College/DHQ Hospital, Gujranwala

Abstract

Objective To compare efficacy of intralesional 5-fluorouracil (5-FU) plus triamcinolone acetonide (TCA) versus intralesional TCA alone in the treatment of keloids.

Methods The study included 100 patients with keloids. Patients were divided into two groups. Randomization was done through lottery method. For each 1 cm area, group A was given intralesional 5-FU 50 mg/ml (0.9ml) plus TCA 40mg/ml (0.1ml) after every 4 weeks and group B was given intralesional TCA 40mg/ml (0.1ml) after every 4 weeks for total period of 12 weeks. Administration of the drugs was continued till the keloid flattened or for a maximum period of 12 weeks. Follow-up was done every 4 weeks for total period of 12 weeks after the administration of last injection. Decrease in total score using Vancouver Scar Scale was calculated.

Results After the completion of study mean reduction in Vancouver Scar Score was -71.18 ± 8.69 in the intralesional 5-FU plus TCA group as compared to -50.80 ± 8.59 in the intralesional TCA group (p=0.001). 5-FU + TCA was efficacious in 98% of cases (group A) and TCA alone in 62% of cases (group B). No serious adverse effects were noticed in either group.

Conclusion Intralesional 5-FU plus TCA is significantly better than intralesional TCA alone in the treatment of keloids.

Key words
Keloids, 5-fluorouracil, triamcinolone acetonide, Vancouver Scar Scale.

Introduction

Cutaneous scars are one of the most frequently occurring conditions. The process of wound repair and restructuring is complicated and various factors contribute to the creation of various types of scars such as hypertrophic, atrophic, or normotrophic. Regulation of connective tissue formation is under the rigorous control of a number of soluble mediators, acting in concert to ensure tissue integrity and homeostasis, during development and repair processes. To ensure a healthy and functional scar, structural proteins and glycoproteins must be deposited and removed at appropriate rate and time. Disruption of the fragile equilibrium between anabolic and catabolic cytokines may lead to extracellular matrix synthesis and deposition.

The term keloid is derived from the Greek word "cheloides" meaning "crab's claw". A keloid is an elevated fibrous scar that extends beyond the

Address for correspondence
Dr. Farah Saleem
Department of Pediatric Dermatology
Institute of Child Health/The Children's Hospital Lahore
Email: farahsaleemleo@hotmail.com

borders of the original wound, does not regress and usually recurs after excision.[1] It occurs due to idiopathic excessive accumulation of collagen in the wound by increased biosynthesis of fibroblasts.[2] The most common sites for developing keloid are sternum, shoulders, earlobes and cheeks.[3] Keloid arises from different skin conditions such as wounds, granulomas, acne, vaccination, earlobe piercing and spontaneously with no definable cause.[4] Till date, keloids pose a challenge to the dermatologists due to their ability to recur in spite of adequate treatment and variable response to different therapies available. The high recurrence rate of keloids has initiated a wide variety of treatments, such as compression therapy, intralesional injections of corticosteroid, methotrexate, bleomycin, radiotherapy, cryosurgery, laser therapy, tamoxifen and tacrolimus.[5] Recent therapies such as pulsed dye laser, interferon alpha 2b and cultured epithelial autografts have also been used. No single therapeutic modality has been found to be very effective for treating them.[5]

Steroids are the mainstay of treatment at present. Triamcinolone acetonide (TCA) acts by inhibiting protein synthesis and fibroblast migration. Some promise in the treatment of keloid has been offered by 5-fluorouracil (5-FU), which is a potent inhibitor of thymidylate synthetase and interferes with pyrimidine metabolism, thus DNA synthesis is blocked.[6] It was found that when used alone, 5-FU did not perform better than steroid. In a study by Prabhu *et al*.[7] the mean reduction in volume of keloid in the 14 patients treated with 5-FU was 57.48% with a standard deviation of 16. In the 15 patients who were treated with TCA, the mean reduction in volume was 71.23%, with a standard deviation of 18.01.[7] However, 5-FU in combination with triamcinolone showed a better efficacy than steroid alone. Sharma *et al*.[8] found good to excellent response in 96% cases treated with a combination of 5-FU and TCA in contrast to 72% cases treated with TCA alone.[8]

Many studies have been conducted in this aspect in developed countries but published data from developing countries like Pakistan are scanty. Small sample size taken in different comparative studies of intralesional 5-FU and TCA done abroad ranged from 28-30 cases.[7,8] In the present study local data with large sample size of 100 cases were generated for better choice of management option. No other study used standard scale to assess accurate results of treatment modalities in keloids. Current study evaluated efficacy by using authentic Vancouver Score.[9]

Methods

A randomized controlled trial was done on patients of either sex, presenting to outpatient Department of Dermatology, Unit II, Mayo Hospital, Lahore. All clinically diagnosed cases of either gender between 20 to 45 years of age, with keloids of duration less than 5 years and size between 1-5 centimeters were included in study after informed consent. Pregnant or lactating mothers, patients having diseases like acromegaly, diabetes mellitus and congestive cardiac disease, on history, physical examination and investigations like blood sugar level and electrocardiography and patients on systemic retinoids and anabolic steroids were excluded.

A total of 100 patients fulfilling the inclusion and exclusion criteria were enrolled. After taking informed consent, demographic data (name, age, sex, marital status, contact number and address) were recorded. Patients were randomized into two groups by lottery method. For each 1 cm area, group A was given intralesional 5-FU, 50 mg/ml (0.9ml) plus TCA, 40mg/ml (0.1ml) after every 4 weeks and group B was given intralesional TCA, 40mg/ml

(0.1ml) after every 4 weeks for total period of 12 weeks. Administration of the drugs was continued till the keloid flattened or for a maximum period of 12 weeks. The patients were followed up every 4th week for total period of 12 weeks after the administration of last injection. Patient's lesions were photographed, with consent of patient. The response of treatment was evaluated by decrease in total score using Vancouver Scar Scale (**Table 1**) at each follow-up visit.

The data were entered and analyzed by using SPSS version 12.0. A quantitative variable like age of patient was presented as mean and standard deviation. Qualitative variables like sex of patient and efficacy were expressed in terms of, frequency and percentages. Efficacy in both treatment groups was compared by using Chi-Square test. P value of <0.05 was considered as statistically significant.

Table 1 Vancouver Scar Scale [9].

Variables	*Scar characteristics*	*Score*
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pigmentation	Normal	0
	Hypopigmentation	1
	Mixed	2
	Hyperpigmentation	3
Pliability	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Ropes	4
	Contracture	5
Height	Flat	0
	< 2mm	1
	2 - 5 mm	2
	>5 mm	3

Results

One hundred patients, 57 (57%) males and 43 (43%) females were enrolled. All of patients completed the study. The age of patients ranged from 20 to 45 years. Mean age in group A was 30.82 ± 8.20 years and in group B was 32.46 ± 6.85 years. Most of the patients were between 20 to 25 years of age (**Table 2**). Majority of males who presented to us with keloids belonged to age group 31-35 while in females presentation of the patients was a decade younger.

In group A, the mean Vancouver Scar Score was 11.16 before and 3.14 after treatment (p = 0.001) whereas in group B, the mean Vancouver Scar Score was 9.80 before and 4.82 after treatment (p = 0.001). Comparison of efficacy between group A and group B is shown in **Table 3**. 5-FU + TCA was efficacious in 98% of cases (group A) and TCA alone in 62% of cases (group B). The results of the mean decrease in Vancouver Scar Score in both the groups are shown in **Table 4**. No recurrence in keloid scar was noticed in any patient. Except pain at the time of injection, no serious adverse effects were noted in either group.

Discussion

In the different published comparative studies, small sample sizes ranging from 28-30 cases were taken.[7,8] Similarly, the Vancouver Scar Score has not been used in these studies to determine the efficacy of various treatment modalities. In our study, large sample size of

Table 2 Cross tabulation of age groups and sex

Age group (years)	*Sex*		*Total*
	Male	*Female*	
20-25	11	19	30
26-30	9	6	15
31-35	16	9	25
36-40	7	5	12
41-45	14	4	18
Total	57	43	100

Table 3 Descriptive statistics of the mean Vancouver Scar Score in both groups (p = 0.001).

	Group A (n=50) Intralesional 5-FU + TCA	*Group B (n=50) Intralesional TCA alone*
Before treatment	11.1600 ± 1.74215	9.8000 ± 1.56492
After treatment	3.1400 ± 0.83324	4.8200 ± 1.11922
P value	0.001	0.001

Table 4 Comparison of efficacy between group A (intralesional 5-FU + TCA) and group B (intralesional TCA alone).

	Group A (n=50)	*Group B (n=50)*
Effective	49 (98%)	31 (62%)
Ineffective	1 (2%)	19 (38%)

Chi-square test=20.250, $p = 0.001$

100 cases was taken and efficacy of drugs was evaluated by using authentic Vancouver Scar Score.[9]

In our study, 57% patients were males while 43% were females. Internationally the occurrence of keloids has an almost equal sex distribution, which is in contrast to our study. The reason behind this may be the social setup in our country, in which less number of females with keloids report to the hospitals. There may be a difference in sex distribution of keloids in this part of the world, but statistically there is lack of epidemiologic studies of keloids in Pakistan and this area needs to be evaluated.

The mean age was same in both the groups. The majority of patients enrolled in our study were below 30 years of age with a peak between 20 and 25 years which is comparable with other studies, carried out in other parts of the world. Berman *et al.*[10] reported that most patients having keloids were younger than 30 years of age. Gauglitz *et al.*[11] also found that the highest incidence of keloids was in the 2nd and 3rd decade of life. In another study conducted in Iran,[12] the keloids were more prevalent between 15 to 30 years of age.

Comparison of efficacy showed that 5FU + TCA was effective in 98% of cases (group A) and TCA alone in 62% of cases in Group B. At final evaluation, mean reduction in the Vancouver Scar Score was -71.18 (±8.69) in the intralesional 5-FU plus TCA group as compared to -50.80 (±8.59) in the intralesional TCA group. ($p = 0.001$).

Fitzpatrick[13] was the first to report experience with TCA plus 5-FU, reporting a 9-year experience administering > 5000 injections to > 1000 patients. He found that by mixing 1mg/ml TCA with 5-FU (by adding 0.1 ml of 10 mg/ml TAC to 0.9 ml of 50mg/ml 5-FU), efficacy was improved and injections were less painful. Patients returned for injections on an average of 5-10 times.[13]

The reason that intralesional TCA alone is less effective than combination therapy with intralesional TCA and 5-FU is that in addition to inhibitory effect on TGF-ß-induced expression of type 1 collagen gene in human fibroblasts, 5-FU has an inhibitory effect on production of thymidylate synthetase, thus blocking DNA synthesis. By inhibition of DNA synthesis in rapidly proliferating and metabolizing cells, apoptosis of fibroblast is increased.[14] In comparison with TAC group, it seems that TAC+5-FU combination is more effective and provides more rapid response with fewer side effects. Apikian and Goodman[15] found that intralesional 5-FU mixed with low dose corticosteroid may be a possible alternative for

the treatment of keloid scars and may have fewer undesirable side effects when compared with intralesional potent corticosteroids alone. Comparable results have been reported by other investigators.[16,17]

Intralesional 5-FU has been used as an adjuvant therapy to intralesional TCA and 585-nm flashlamp-pumped pulsed dye laser (5-FU+ TCA+ PDL) in majority of studies in the prevention, as well as, the treatment of keloids.[17,18]

Asilian *et al.*[19] (2006) examined the effectiveness of a combination of intralesional steroid, 5-FU, and pulsed dye laser in the treatment of hypertrophic scars and keloids. A total of 69 patients were randomly assigned to treatment with intralesional TCA, intralesional TCA plus intralesional 5-FU, and TCA, 5-FU and pulse-dye laser treatment. The investigators reported that, after 12 weeks, good to excellent improvement was reported by a blinded observer in 15% of subjects treated with TCA alone, 40% of subjects treated with TA+ 5-FU, and 70% of subjects treated with all 3 modalities.[19]

This shows that intralesional 5-FU gives good results when used as an adjuvant therapy to intralesional TCA and pulse-dye laser, when given in proper dose according to the size of the lesion. It results in rapid reduction in size and symptoms of keloids.

Conclusion

In the treatment of keloids intralesional TCA is efficacious in almost two third of cases while combination of intralesional 5-FU and TCA provides statistically better results in almost all the patients.

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