

Intralesional triamcinolone alone and in combination with 5-fluorouracil for the treatment of Keloid and Hypertrophic scars

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Abstract

Objective: To compare the use of intralesional triamcinolone acetonide and its combination with 5 fluorouracil in the treatment of keloid and hypertrophic scars in terms of reduction in initial height of the scar.

Methods: The randomised controlled trial was conducted at the Department of Plastic Surgery, King Edward Medical University, Lahore, from March 2011 to December 2012. It comprised patients of both genders having keloids or hypertrophic scars (1cm to 5cm in size) having no history of treatment for the scars in preceding 6 months. Those who were pregnant, planning pregnancy or lactating were excluded. The subjects were divided into two groups: Group A received intralesional triamcinolone acetonide alone; and Group B received triamcinolone acetonide + 5 fluorouracil. Eight injections were given at weekly interval. Scars were assessed 4 weeks after the completion of treatment on a five-point scale. SPSS 16 was used for statistical analysis.

Results: The 150 subjects in the study were divided into two equal groups of 75(50%) each. Good to excellent results were seen in 51(68%) cases in Group A compared to 63(84%) in Group B. Frequency of complications was 18(24%) and 6(8%) in Group A and Group B respectively.

Conclusion: Combination of triamcinolone acetonide and 5 fluorouracil is superior to triamcinolone acetonide therapy in the treatment of keloids and hypertrophic scars.

Keywords: 5-Fluorouracil, Hypertrophic scar, Keloid. (JPMA 64: 1003; 2014)

Introduction

Healing of wounds is a complex physiologic response to trauma. Derangements of this orderly process lead to scars that are exuberant. However, spontaneous keloids may arise without a history of trauma to a particular site. The exact aetiology is not understood, but most likely entails genetic and environmental factors.¹ Hypertrophic scars remain entirely inside the limits of the original wound and have shown spontaneous regression. However, keloids continue to grow and extend further than the wound boundary, but unlike malignant tumours do not reach outside the dermis and thus are benign lesions.² The incidence of keloid in dark-skinned people is estimated to be 3 to 20 times compared to light-skinned people.³

Physical and psychological problems are common in patients with these conditions. It has been said that the less is known about a disease, the more therapeutic modalities seem to be available. This universal medical truth certainly applies to keloids.⁴ Despite intralesional steroid administration and other multimodal treatment strategies, keloids are notorious for recurrence. With corticosteroid injection alone partial recurrence was

observed in one-third of the cases after 1 year, whereas after 5 years, the recurrence rate was 50 per cent.⁵

These scars have been shown to exist in hypermetabolic state so use of antineoplastic modality is logical. 5-fluorouracil (5-FU) is a pyrimidine analogue having antimetabolite activity. It has been confirmed that 5-FU stops fibroblast proliferation in tissue culture.⁶ Reports suggest that low-dose intralesional 5-FU can be used to treat these undesirable scars.⁷ Combining corticosteroid injections with 5-FU, pulsed dye laser, and cryotherapy has been reported to be more beneficial than corticosteroid injection monotherapy, although there are too few randomised controlled trials testing these issues to be able to draw solid conclusions.⁸ Thus, conclusive evidence about the superiority of 5-FU+ triamcinolone acetonide (TAC) is still lacking. To date, the use of intralesional triamcinolone represents the therapy of choice for small and younger keloids as well as hypertrophic scars.⁹

The rationale of this study was to investigate the pre-eminence of intralesional TAC+5-FU over TAC alone so that a better treatment protocol can be recommended to manage hypertrophic scars and keloids. The objective of the study was to compare the use of intralesional TAC and TAC+ 5-FU in the treatment of keloid and hypertrophic scars in terms of reduction in initial height of the scar and frequency of the complications like skin atrophy (thinning

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of the skin over the scar area) and telangiectasias (dilated superficial blood vessels around scar).

Patients and Methods

The randomised controlled trial was conducted at the Department of Plastic Surgery, King Edward Medical University (KEMU), Lahore, from March 2011 to December 2012. The sample size was calculated with 80% power of test, 99% confidence interval (CI) and taking expected percentage of effectiveness in both groups i.e. 15% in TAC group and 40% in TAC + 5-FU group in the treatment of keloid and hypertrophic scars.¹⁰ Patients of both genders with age above 12 years having keloid or hypertrophic scar from 1cm to 5cm in size, measured clinically by a scale, were included in the study. Patients having history of treatment for scar management in the preceding 6 months; history of chronic renal failure or serum creatinine >1.2mg/dl, abnormal liver function tests (Alanine transaminase [ALT] >35IU) and abnormal complete blood count (CBC) (white blood cells [WBC] < 4 or >11000 cells) and patients who were pregnant, planning pregnancy or lactating were excluded from the study.

After approval from the departmental ethics committee, 150 patients fulfilling the inclusion criteria were randomly selected using random number table. Prior to inclusion, informed written consent was taken from each patient. Patients' demographic details were collected by filling the relevant proforma. Patients were divided randomly into 2 groups, again by using the random number table, Group A and Group B with 75 patients in each group. Group A had patients of intralesional TAC alone, while Group B had patients of combination of intralesional TAC and 5-FU. In all patients, baseline assessment was done before the initiation of treatment by filling the proforma and all lesions were photographed.

All patients were injected with local anaesthetic, 1% xylocaine, with a 3cc syringe by entering the skin through the scar tissue. In Group A, intralesional TAC 10mg (0.25ml of 40mg/ml TAC diluted with 0.75ml injectable normal saline) was administered once weekly for a total of 8 sessions.⁹ In Group B, intralesional injection of TAC 4mg (0.1ml of 40 mg/ml TAC) mixed with 5-FU 45mg (0.9 ml of 50 mg/ml 5-FU) was administered once weekly for a total of eight sessions. The solution was injected in the body of scar till slight blanching was clinically evident. For the larger lesions, the dose was increased but not more than 2ml per session.⁹ Indurated part of scar was injected and those that needed multiple injection sites per scar were separated by approximately 1cm. Assessment of patient was done at 4th and 8th week of treatment and finally after 4 weeks of the completion of treatment.

Scar was assessed on a five-point observer scar assessment scale, with 0 = no improvement (no reduction in height of the scar), 1= poor (0-25% reduction in height), 2= fair (25-50% reduction in height), 3= good (50-75% reduction in height) and 4= excellent (75-100% reduction in height). Effectiveness was termed with more than 50% reduction in initial scar height and complications as having skin atrophy and telangiectasia after treatment. Patients were followed up to look for recurrence which was defined as reappearance of raised scar above the level of adjacent skin limited to or extending beyond the confines of original wound up to a maximum follow-up of six months. All the information was collected through a proforma. SPSS Version 16.0 was used for analysis. Effectiveness and complications (skin atrophy and telangiectasias) were presented as frequency and percentage. Chi square test was used to compare the effectiveness and frequency of complications in both groups. Repeated measure analysis of variance (ANOVA) was used to see the difference within and between groups. Analysis of covariance (ANCOVA) was used to account for the initial scar height as covariate, taking complications (Yes or No) and groups (TAC alone or TAC+5FU) as fixed factors and final height of the scar as the dependent variable. $P \leq 0.05$ was considered significant.

Results

Of the 150 patients in the study, 65(43.3%) were males and 85(56.6%) were females. The mean age was

Table-1: Effectiveness and complications in two groups.

	Group of the patient				P value
	TAC alone (n=75) Yes	NO	TAC +5FU (n=75) Yes	No	
>50% improvement	51(68%)	24(32%)	63(84%)	12(16%)	0.035
Complications	18(24%)	57(76%)	6(8%)	69(92%)	0.013

Chi square; $p > 0.05$ considered significant

TAC: Triamcinolone acetonide

5-FU: 5 Fluorouracil.

Table-2: Confounding effect of gender on effectiveness and complications.

Gender of the Patient	Group of the patient				P value
	TAC alone (n=75) Yes	NO	TAC +5FU (n=75) Yes	No	
Female (n=85)					
>50% improvement	34(75.6%)	11(24.4%)	36(90%)	4(10%)	0.81
Complications	13(28.9%)	32(71.1%)	4(10%)	36(90%)	0.03
Male(n=65)					
>50% improvement	17(56.7%)	13(43.3%)	27(77.1%)	8(22.9%)	0.78
Complications	5(16.7%)	25(83.3%)	2(5.7%)	33(94.3%)	0.156

Chi square; $p > 0.05$ considering significant

TAC: Triamcinolone acetonide

5-FU: 5 Fluorouracil.

Table-3: Confounding effect of type of scar on effectiveness and complications.

Type of the scar	Group of the patient				P value
Hypertrophic scar(n=92)	TAC alone (n=75)		TAC +5FU (n=75)		
	Yes	NO	Yes	No	
>50% improvement	31(73.80%)	11(26.19%)	46(88.46%)	4(7.69%)	0.024
Complications	8(19.04%)	34(80.95%)	5(10%)	45(90%)	0.243
Keloids(n=58)					
>50% improvement	20(60.60%)	13(39.39%)	17(68%)	8(32%)	0.594
Complications	10(30.30%)	23(69.69%)	1(4%)	24(96%)	0.016

Chi square; p>0.05 considered significant

TAC: Triamcinolone acetonide

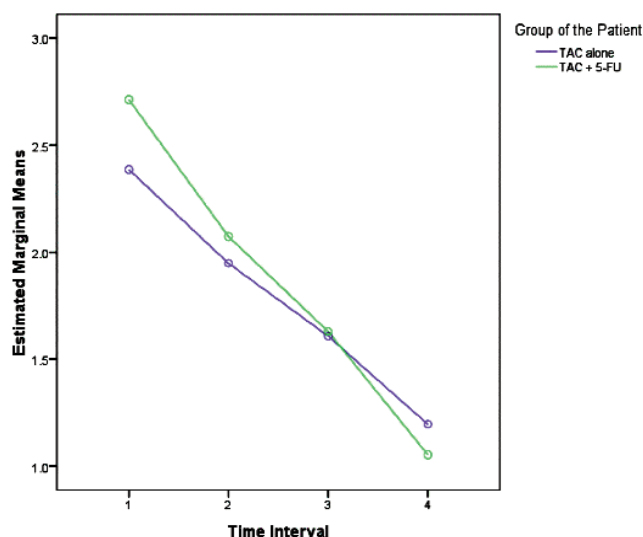
5-FU: 5 Fluorouracil.

Table-4: Scar height over time.

	Group of the patient		Total (n=150)
	TAC alone (n=75)	TAC +5FU (n=75)	
Original height of the scar	2.387cm±0.9348	2.713cm±0.9786	2.550cm±0.9677
Height at 4 weeks	1.948cm±0.8199	2.073cm±0.7509	2.011cm±0.7860
Height at 8 weeks	1.608cm±0.8183	1.629cm±0.6898	1.619cm±0.7544
Height at 12 weeks	1.196cm±0.8825	1.053cm±0.5313	1.125cm±0.7294

TAC: Triamcinolone acetonide

5-FU: 5 Fluorouracil.

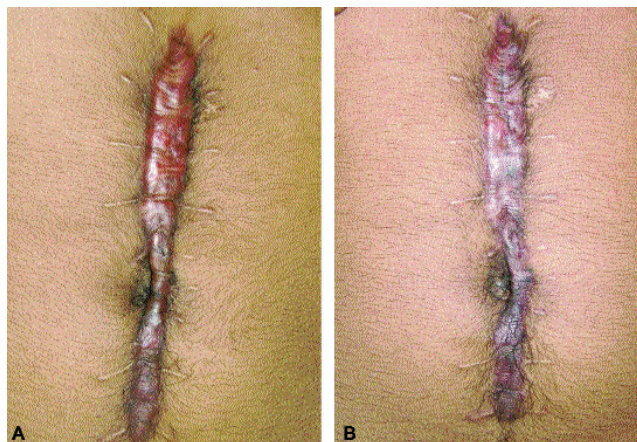


TAC: Triamcinolone acetonide

5-FU: 5 Fluorouracil

Figure-1: Reduction in height of the scar over time in two groups.

29.93±8.946 years in TAC group and 28.96±9.623 years in TAC+5FU group (p=0.522). Good to excellent results were seen in 51(68%) cases in Group A compared to 63(84%) in Group B. Frequency of complications was 18(24%) and

**Figure-2:** A): Before Treatment. B): 12 Weeks Post Treatment.

This was a 30-year-old male with laprotomy wound hypertrophic scar for last one-and-a-half years. He was treated with triamcinolone acetonide alone. The patient had symptomatic relief at the end of the treatment.

**Figure-3:** A): Before Treatment. B): At the End of Treatment.

A 20-year-old male with keloid right shoulder area. He had marked improvement in symptoms and appearance at the end of the treatment with 5 Fluorouracil and triamcinolone acetonide, and the scar was even better looking at 6 months of follow-up.

6(8%) in Group A and Group B respectively (Table-1). The confounding effect of gender on effectiveness and complications was noted separately (Table-2). Besides, 90(60%) patients had hypertrophic scars and 60(40%) had keloids. The confounding effect of type of scar on effectiveness and complications was also noted (Table-3). Descriptive statistics for the height of the scar were also observed (Table-4). Repeated measure ANOVA showed



Figure-4: A): Before Treatment. B): At the End of Treatment.

This 40-year-old female had post-burn hypertrophic scarring face for two years. She had marked reduction in scar height at the end of the treatment with 5-Fluorouracil and triamcinolone acetonide, and had even better appearance at 6 months of follow-up.

statistical significance for height ($p < 0.001$) and factor ($p < 0.001$). The mean reduction in the scar height and the response time to the two treatment modalities was kept under observation (Figure-1). ANCOVA showed there was statistically strong evidence that the final scar height was better in TAC+5FU group after accounting for the initial scar height, ($F[1,3.559] = 12.505$; $p < 0.001$). Also, there was statistically strong evidence that final scar height was better in patients having complications after accounting for the initial scar height ($F[1,1.180] = 3.924$; $p < 0.049$). There were no recurrences noted over the 6-month follow-up.

Discussion

Keloids and hypertrophic scars result from abnormal healing of skin injury. Because of the significant functional and psychological burdens of such conditions, patients frequently seek medical treatment. The efficacy of corticosteroid injections in the treatment of keloids and hypertrophic scars has been well recognised.

TAC is one of the most frequently used corticosteroids. The dose and treatment intervals have a range of 10-40mg/mL given at intermission of 4 to 6 weeks for quite a few months or until the scar is evened out. Despite the fact that intralesional TAC injection has shown 50% to 100% clinical efficacy, the result has not been satisfactory.⁸ Moreover, TAC use is associated with numerous unpleasant effects, including, telangiectasia atrophy, and pigmentary changes, which are not desirable for the majority of patients.¹¹

5-FU is a fluorinated pyrimidine that acts as an

antimetabolic agent. It inhibits thymidylate synthase and interferes with ribonucleic acid (RNA) synthesis and function. Recent evidence suggests that 5-FU selectively blocks collagen synthesis, which may augment its anti-scar role.¹² It has been unveiled that 5-FU administered intralesionally weekly or fortnightly to hypertrophic scars and keloids is effective in reducing the activity of fibroblasts.⁸ Intralesional 5-FU administration is safe, provided the recommended upper limit of the dose is not breached; the toxicity is related to intravenous dosage, not subcutaneous.¹³ Side effects like erythema and ulceration are common when pure 5-FU is used. Small concentration of TAC is added in order to reduce these local side effects. This small amount of TAC has no role in efficacy.¹⁴ In the current study, 45mg of 5-FU (0.9ml of 250mg/5ml) was mixed with 4mg TAC (0.1 ml of 40mg/1ml). This combination is documented as more effective and gives rapid response with fewer side effects.¹⁵

Initially, Fitzpatrick published his 9-year familiarity with the use of TAC + 5-FU. He had the experience of over 5000 injections to more than 1000 patients. He reported that addition of TAC to 5-FU produced more effective results and reduced the pain. Combination was made by addition of 0.1mL of 10mg/mL TAC to 0.9mL of 50mg/mL 5-FU. Injections were repeated for a mean of 5 to 10 times. Dosage of drug and duration of exposure had been found as major determinants of fibroblast degeneration.¹⁶

Thorough search of the literature concerning the use of corticosteroids in the treatment of keloid reveals that a dose of 10-40 mg/mL TAC is necessary to be effectual in keloid or hypertrophic scar.⁹ The concentration of triamcinolone would be 4mg/ml in a mixture of TAC and 5-FU. This concentration is not likely to have any effect on reducing the size of the lesion, but it reduces 5-FU-induced inflammation.¹⁷ The results of the current study in the TAC+5-FU group are comparable to those reported earlier. The representative cases in the two groups make the point clear (Figures-2,3,4).

It was observed by a study that using combination of TAC+5FU resulted in more than 50% improvement in about 80% patients. In comparison with TAC group, it looks as if TAC+5-FU combination is more effectual and offers a faster response with fewer if not without side effects.¹⁸ The findings of the current study are also in accordance with another study which proposed that intralesional 5-FU combined with low-dose corticosteroid is an option for the treatment of keloid scars and have less undesirable effects compared to intralesional corticosteroids alone.^{17,19}

Another study²⁰ observed 85% of patients with more than 50% improvement, but significant recurrence was seen in 45% and ulceration in 30% cases in 12-month follow-up. In the current study, recurrence was not noted probably due to shorter follow-up duration of 6 months. One study¹⁰ compared 5-FU + TAC with TAC alone. It observed good to excellent (>50%) improvement in 20% of the patients in TAC alone group, and 55% of the patients in the combination group, and on the observer assessment scale good to excellent response was reported in 15% in TAC alone, and 40% in the combination therapy. This 12-week follow-up study showed improvement in all parameters among both groups which are consistent with the current study in which TAC group patients had efficacy of 68% with observer assessment scale, but with side effects in 24% which are comparatively high and unacceptable for the patients.

No serious systemic side effects were observed among TAC + 5-FU group in the current study. Based on pharmacokinetic studies, 5-FU remains in the soft tissue for less than 10 days. Once taken up in the bloodstream, it is degraded within 20 minutes. The metabolites are excreted by the kidney. Drug toxicity is related to intravenous dosing; not subcutaneous. Systemic 5-FU can cause anaemia, leukopenia, and thrombocytopenia. Although dose of 5-FU was not more than 90mg at each injection session, the administration of higher doses has been described without development of any undesirable haematologic effects.⁷

One limitation of the current study is the short duration of follow-up. Even though most reports do not show results beyond 1 year after treatment, it is apparent that keloid reappearance can take place in the years to follow. Logistically, lasting follow-up in this type of study is difficult. The second problem found was the pain experienced by the recipients during local anaesthetic insertion. Although local anaesthetic was introduced using 27G needle due to unavailability of 30G needle, but the pain experienced by the patients using 30G needle is less, as documented by other studies.^{14,20}

Conclusion

The combination therapy of 5FU+TAC is more efficacious having fewer undesirable effects compared to TAC alone in the treatment of both hypertrophic scars and keloids.

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