Comparison of Intralesional Triamcinolone Acetonide, 5-Fluorouracil, and Their Combination for the Treatment of Keloids

Sunil Srivastava,¹ Aditya Nanasaheb Patil,^{1,*}
Chaitra Prakash,² and Hiranmayi Kumari¹

Departments of ¹Plastic Surgery and ²Dermatology, Sawai Man Singh Medical College and Hospital, Rajasthan University of Health Sciences, Jaipur, India.

Objective: Despite the myriad options available, there is no universally accepted treatment for keloids. Our objective was to compare three regimens and establish superiority in terms of objective and subjective outcomes.

Approach: In this randomized parallel group study, 60 patients were enrolled and randomly allocated to three groups. Patients received intralesional injections of triamcinolone acetonide (TAC) in Group TAC, 5-fluorouracil (5FU) in Group 5FU, and a combination in Group T + F every 3 weeks till 24 weeks or till the keloid resolved.

Results: There was a reduction in all parameters at every successive assessment in all three groups. Improvement in terms of height, vascularity, and pliability was fastest with 5FU, TAC, and T + F group, respectively, which was statistically significant. Decrease in pigmentation was significantly faster with T+F. Reduction in pruritus, however, was significantly faster with 5FU than the other groups, but the difference in reduction of pain among the three groups was not significant. Telangiectasias and skin atrophy were seen most commonly in TAC group, while skin ulceration was a common problem in 5FU group.

Conclusion: TAC, 5FU, and their combination are all effective in keloid scars. A combination of TAC +5FU seems to offer the balanced benefit of faster and more efficacious response with lesser adverse effects when compared to individual drugs.

Keywords: keloid, intralesional, triamcinolone, 5-fluorouracil, combination

INTRODUCTION

WOUND HEALING OCCURS as a result of a close interplay between many factors, both internal and external. However, despite ideal conditions, not always does a wound heal as expected. At one end of the spectrum of such deviant healing are keloids that represent an exuberant healing response. However, keloids are also known to occur spontaneously without an inciting cause. An absence of a cognizable traumatic event emphasizes the role of genetic and environmental factors. The exact cause for this disorder re-

mains elusive, despite ongoing research and hypotheses.¹

Keloids are known for a lack of standardized treatment and a high propensity for recurrence.² This is evident in the wide range of available treatment modalities like surgical excision, cryotherapy, laser therapy, low-dose radiation, silicone sheeting, topical retinoids, and intralesional injections of steroid, 5-fluorouracil (5FU), and bleomycin being employed.³ All of these regimens are empirical, none of which guarantee a definite cure.

Aditya Nanasaheb Patil, MS

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*Correspondence: Department of Plastic Surgery, SMS Medical College and Hospital, JLN Marg, Jaipur 302004 (Rajasthan), India
(e-mail: drpatiladitya@gmail.com).

Triamcinolone acetonide (TAC), a long-acting glucocorticoid, has been the most popular drug and can presently be considered the gold standard in keloid treatment, alone or in combination.³⁻⁵ A clinical efficacy ranging from 50% to 100% and a recurrence rate ranging between 9% and 50% have been reported.^{6,7} Moreover, the time for complete response is not consistent and a long-term use can lead to complications like telangiectasia and skin atrophy. 5FU, a pyrimidine analogue, was first introduced in the treatment of keloid by Fitzpatrick who published his results in 1999.⁸ Since then, several studies have documented its efficacy in keloids.⁹ 5FU has a comparatively faster response in scar flattening.¹⁰ Combining TAC with 5FU has been suggested to have a rapid response in terms of scar flattening with an added advantage of fewer side effects.^{11,12} Numerous studies have compared this combination with other drugs and modalities, but these studies cannot be directly compared to each other owing to inconstant outcome variables. To the best of our knowledge, there is no study that simultaneously compares these two drugs alone and as a combination.

This randomized study was undertaken with the objective of comparing these three regimens viz. triamcinolone alone, 5FU alone, and a combination of triamcinolone and 5FU in terms of subjective and objective outcomes; adverse effects were also noted. A short review and results of the study are discussed.

CLINICAL PROBLEM ADDRESSED

A lot of confusion exists regarding choice of treatment while addressing keloids, which include, but are not limited to, surgical excision, cryotherapy, laser therapy, low-dose radiation, silicone sheeting, topical retinoids, and intralesional injections of steroid, 5FU, and bleomycin.³ Sadly, however, none of these guarantee a definite cure. Our study attempts to throw more light in this direction and help in choosing, or avoiding, some of these regimens.

MATERIALS AND METHODS

This was a single-blind, randomized parallel group study conducted in the Department of Plastic Surgery, Sawai Man Singh Medical College and Hospital, Jaipur. Patients were enrolled between January 2016 and June 2016 from the outpatient clinic. The study protocol was approved by the institutional Ethics Review Committee. Informed consent was obtained from all the participants.

Inclusion criteria included patients aged 18 to 60 years with keloids of size 1 to 10 cm in greatest dimension and of >6-month duration. Keloids were diagnosed on the basis of history and clinical exami-

nation, and were differentiated from hypertrophic scars, the latter of which were not included in the study. Females who were pregnant or were planning pregnancy were excluded. Patients who had received treatment for the same keloid in the past 12 months and those who had active inflammation, infection, or ulcer in or around the keloid were not included. Immunosuppressed patients, patients with chronic inflammatory diseases, and those with history of renal or liver failure were also excluded. Blood investigations, including complete blood count and renal and liver function tests, were done before inclusion in the study. These tests were repeated at the fourth visit (12th week) and last visit (30th week).

Detailed history and demographic parameters were recorded, including etiology and region of keloid. Etiology was divided into "infective," "traumatic," and, if there was no discernible etiology, "spontaneous."

A total of 60 patients were enrolled for the study and were randomly allocated to one of three groups using a computer-generated random sequence. A single contiguous keloid per patient was considered for the study. Keloids in Group TAC received intralesional TAC 40 mg/mL, keloids in Group 5FU received intralesional 5FU 50 mg/mL, and those in Group T+F received intralesional injection of a combination of TAC (40 mg/mL) and 5FU (50 mg/mL) in a ratio of 1:9. The drugs used were undiluted, but for the said combination.

Injections were made with 27-gauge insulin syringe such that volume injected did not exceed 0.5 mL per square centimeter of keloid. Whenever necessary, multiple pricks were made 1 cm apart to ensure complete and uniform distribution. A maximum of 2 mL was injected per session. Injections were administered every 3 weeks till 24 weeks or till the keloid resolved, whichever was earlier. Keloid was defined as "resolved" when a total score of 2 or less was achieved on Vancouver Scar Scale (VSS) (vide infra). No local infiltration of anesthetics was done; analgesic was administered orally. Patients received no other therapies like scar massage, laser therapy, or pressure garments during the course of study.

All patients were evaluated before every injection and a final evaluation was performed 30 weeks after first dose. All evaluations were done by two independent observers who were blinded to the treatment groups. Evaluation was done objectively using VSS and subjectively by assessing pain and pruritus. Adverse effects at the time of injection and other complaints during the course of treatment were also recorded.

VSS was originally designed by Sullivan *et al.* to assess burn scars, which has since been ex-

Table 1. Baseline characteristics of patients

Variable	TAC	5FU	T+F	p ^a
Age (mean ± SD), years	26.35 ± 6.11	27.55 ± 8.54	29.9 ± 10.19	0.41
Sex, n (%)				
Female	12 (60)	10 (50)	12 (60)	0.76
Male	8 (40)	10 (50)	8 (40)	
Etiology, n (%)				
Infective	12 (60)	11 (55)	14 (70)	0.64
Traumatic	6 (30)	5 (25)	5 (25)	
Spontaneous	2 (10)	4 (20)	1 (5)	
Region, n (%)				
Presternal	11 (55)	12 (60)	9 (45)	0.69
Trunk	5 (25)	2 (10)	7 (35)	
Extremities	3 (15)	4 (20)	3 (15)	
Face	1 (5)	2 (10)	1 (5)	

^aAll *p*-values were greater than 0.05 (no statistically significant difference).

5FU, 5-fluorouracil; TAC, triamcinolone acetonide.

tended to include other scars as well.^{13,14} For VSS, keloid height was measured with calipers; pliability was assessed by palpation; vascularity was assessed by visual inspection; and pigmentation was scored after blanching and comparing it with the surrounding skin. Blanching was achieved using a piece of clear plastic sheet. Pain and pruritus were scored on a three-point scale as follows: 0 = no pain/pruritus; 1 = mild; 2 = moderate; and 3 = severe pain/pruritus.

Comparative survival analysis between the three groups was done using Kaplan–Meier curves to compare rate of improvement. Wilcoxon test was used to compare survival distribution among groups with the test statistics based on differences in group mean scores. Pain and pruritus scores were compared between the three groups using chi-square test for qualitative analysis and analysis of variance for difference in means of groups. Statistical analysis was carried out with SPSS software for Windows

Version 23.0 (Armonk, NY). A *p*-value of <0.05 was considered to be significant.

RESULTS

A total of 60 patients were enrolled in the study and were randomly distributed in three groups of 20 each. The youngest patient included in the study was 18 years old and the oldest was 56 years old. There were 26 males and 34 females in the study. Infective etiology (*n* = 37) was the commonest etiology followed by traumatic (*n* = 16) and spontaneous (*n* = 7). Presternal region (*n* = 32) was the most frequently involved region, followed by trunk (*n* = 14), extremities (*n* = 10), and face (*n* = 4). The baseline characteristics in terms of age, sex, etiology, and region involved were comparable in all three groups (Table 1).

There was no significant difference in baseline preinjection scores of pain and pruritus and all four parameters of VSS (Table 2).

Mean preinjection VSS scores for all treatment groups at every evaluation are presented in Table 2. There was a reduction in height, vascularity, pliability, and pigmentation at every successive assessment in all three groups, which was maintained till the final evaluation. The rate of improvement can be seen in the Kaplan–Meier curves (Fig. 1). 5FU had the lowest survival curves for height, TAC for vascularity, and T + F for both pliability and pigmentation. Statistically significant differences among groups in terms of reduction of vascularity and pliability were noted after the sixth week, while that of height and pigmentation were noted after the third week (Table 2).

Comparison using Wilcoxon test showed that improvement in terms of height, vascularity, and pliability was fastest with 5FU, TAC, and T + F group, respectively, which was statistically signif-

Table 2. Mean preinjection Vancouver Scar Scale scores

		Mean Preinjection VSS Scores ^a									
VSS Parameters	Group	0 Week	3 Weeks	6 Weeks	9 Weeks	12 Weeks	15 Weeks	18 Weeks	21 Weeks	24 Weeks	30 Weeks
Height	TAC	1.7 ± 0.57	1.7 ± 0.57	1.65 ± 0.49	1.65 ± 0.50	1.6 ± 0.50	1.4 ± 0.60	1.2 ± 0.70	0.75 ± 0.55	0.65 ± 0.51	0.61 ± 0.45
	5FU	1.8 ± 0.41	1.8 ± 0.41	1.65 ± 0.49	1.25 ± 0.55	1 ± 0.56	0.85 ± 0.59	0.45 ± 0.51	0.3 ± 0.47	0.2 ± 0.41	0.2 ± 0.41
	T + F	1.9 ± 0.31	1.9 ± 0.31	1.9 ± 0.31	1.8 ± 0.41	1.4 ± 0.50	1.05 ± 0.39	0.9 ± 0.31	0.7 ± 0.47	0.35 ± 0.49	0.3 ± 0.47
Vascularity	TAC	1.85 ± 0.37	1.85 ± 0.37	1.75 ± 0.44	1.4 ± 0.50	1.05 ± 0.39	0.75 ± 0.44	0.55 ± 0.51	0.25 ± 0.44	0.15 ± 0.37	0.15 ± 0.37
	5FU	1.9 ± 0.31	1.9 ± 0.31	1.9 ± 0.31	1.9 ± 0.31	1.7 ± 0.47	1.2 ± 0.41	0.95 ± 0.22	0.9 ± 0.31	0.55 ± 0.51	0.55 ± 0.51
	T + F	2 ± 0	2 ± 0	2 ± 0	1.55 ± 0.51	1.1 ± 0.31	1 ± 0	0.9 ± 0.31	0.5 ± 0.51	0.25 ± 0.44	0.25 ± 0.44
Pliability	TAC	2.8 ± 0.41	2.8 ± 0.41	2.6 ± 0.50	2.2 ± 0.52	1.85 ± 0.49	1.6 ± 0.50	1.2 ± 0.52	1.05 ± 0.51	0.8 ± 0.52	0.75 ± 0.44
	5FU	2.65 ± 0.49	2.65 ± 0.49	2.45 ± 0.51	2.1 ± 0.55	1.6 ± 0.50	1.4 ± 0.50	1.1 ± 0.64	0.65 ± 0.49	0.5 ± 0.51	0.5 ± 0.51
	T + F	2.8 ± 0.41	2.65 ± 0.49	2.05 ± 0.69	1.6 ± 0.75	1.2 ± 0.52	1 ± 0.73	0.8 ± 0.62	0.45 ± 0.51	0.35 ± 0.49	0.35 ± 0.49
Pigmentation	TAC	1.85 ± 0.37	1.85 ± 0.37	1.85 ± 0.37	1.8 ± 0.41	1.65 ± 0.49	1.4 ± 0.5	1.05 ± 0.22	1 ± 0.32	0.7 ± 0.47	0.7 ± 0.47
	5FU	1.8 ± 0.41	1.8 ± 0.41	1.8 ± 0.41	1.75 ± 0.44	1.35 ± 0.49	1.1 ± 0.31	1 ± 0	0.65 ± 0.49	0.6 ± 0.50	0.6 ± 0.50
	T + F	1.85 ± 0.37	1.85 ± 0.37	1.7 ± 0.47	1.35 ± 0.59	0.95 ± 0.22	0.85 ± 0.37	0.7 ± 0.47	0.35 ± 0.49	0.15 ± 0.37	0.15 ± 0.37

^aValues denoted as mean ± SD.

VSS, Vancouver Scar Scale.

Figure 1. Kaplan–Meier survival curves for height, vascularity, pliability, and pigmentation.

icant. Decrease in pigmentation was seen faster with T + F than with individual drugs alone, which was highly significant.

Pain and pruritus consistently reduced at every successive assessment in all groups (Table 3). The difference in reduction of pain among the three

groups was not significant. Reduction in pruritus, however, was significantly faster with 5FU than the other groups.

Telangiectasias and skin atrophy were seen most frequently in the TAC group. Skin ulceration was a common problem in the 5FU group (Fig. 2),

Table 3. Mean preinjection scores for subjective parameters

Subjective Parameter	Group	Mean Preinjection Scores ^a									
		0 Week	3 Weeks	6 Weeks	9 Weeks	12 Weeks	15 Weeks	18 Weeks	21 Weeks	24 Weeks	30 Weeks
Pain	TAC	2.05 ± 0.89	1.8 ± 0.70	1.2 ± 0.62	0.65 ± 0.59	0.35 ± 0.59	0.15 ± 0.49	0.05 ± 0.22	0 ± 0	0 ± 0	0 ± 0
	5FU	2.3 ± 0.86	1.9 ± 0.72	1.35 ± 0.67	0.8 ± 0.62	0.4 ± 0.50	0.2 ± 0.41	0.1 ± 0.31	0 ± 0	0 ± 0	0 ± 0
	T + F	2.55 ± 0.69	2.25 ± 0.79	1.6 ± 0.75	1.05 ± 0.83	0.6 ± 0.75	0.4 ± 0.50	0.2 ± 0.41	0.1 ± 0.31	0 ± 0	0 ± 0
Pruritus	TAC	2.75 ± 0.44	2.75 ± 0.44	2.5 ± 0.61	2.15 ± 0.59	1.75 ± 0.64	1.3 ± 0.66	1.05 ± 0.69	0.65 ± 0.59	0.35 ± 0.49	0.30 ± 0.45
	5FU	2.85 ± 0.37	2.35 ± 0.49	1.7 ± 0.66	1.1 ± 0.64	0.85 ± 0.59	0.35 ± 0.59	0.1 ± 0.31	0.05 ± 0.22	0.05 ± 0.22	0.05 ± 0.22
	T + F	2.7 ± 0.47	2.55 ± 0.51	2.2 ± 0.52	1.65 ± 0.67	1.25 ± 0.72	0.9 ± 0.64	0.55 ± 0.60	0.3 ± 0.57	0.2 ± 0.52	0.2 ± 0.52

^aValues denoted as mean ± SD.

Figure 2. (a and b) Ulceration following intralesional 5FU injection. 5FU, 5-fluorouracil.

less in the T + F group, and nonexistent in the TAC group. Systemic adverse effects in the form of anemia, leucopenia, or thrombocytopenia were not noted in any patient. No other abnormalities were noted in any other blood investigations. A summary of adverse effects observed in all groups is summarized in Table 4. Pain at injection site was a common problem in the 5FU group (140/166 injection episodes, 84%) compared to the TAC (42/170, 24%) and T + F (58/168, 34%) groups.

DISCUSSION

Alibert in 1806 first coined the word “keloid” to illustrate the way the lesions invaded surrounding normal tissue.¹⁵ They are a cause of cosmetic, physical, as well as psychological embarrassment to patients.⁸ Available literature provides a plethora of treatment options, none of which have been shown to be efficacious beyond doubt.

Intralesional injection of TAC acts in multiple ways, some of which are by decreasing fibroblast proliferation, increasing collagen disintegration, suppressing of inflammation, and decreasing endothelial budding.^{16–19} In addition, it has been noted to cause a significant reduction in the levels of alpha-1-antitrypsin and alpha-2-macroglobulin

levels, which tend to be greater in keloidal tissue and are natural inhibitors of collagenase in human skin.^{20,21} A varying dose of 10–40 mg/mL has been described in literature, necessary to be effective. We chose a dose of 40 mg/mL for our study. The most frequent adverse effects linked to TAC are telangiectasia, skin atrophy, and altered pigmentation.²²

5FU is an antimetabolite, which interferes with RNA synthesis and consequently inhibits fibroblast proliferation. In addition, it also has an inhibitory effect on transforming growth factor (TGF)- β -induced expression of the type I collagen gene.²³ DNA and RNA synthesis are affected at several levels, including inhibition of thymidylate synthetase.^{24,25} 5FU can be administered intralesionally in a dose of 50 mg/mL and has shown favorable results.²⁶ No systemic complications of 5-FU, such as anemia, leucopenia, and thrombocytopenia, have been reported, but the common locally encountered adverse effects include pain at injection site, ulceration, burning, and hyperpigmentation.²⁷

As a combination, TAC has been added to 5FU in a ratio of 1:9, which translates to an absolute TAC concentration of 4 mg/mL.^{27,28} This dose may not be sufficient by itself in scar regression, but it most likely plays a different role by countering the adverse effects of 5FU by its anti-inflammatory nature. Consequently, it is hypothesized that the benefit of faster response of 5FU can be obtained with this combination, while avoiding adverse effects of the individual drugs.

There is no consensus regarding the treatment interval. TAC has been given with an interval varying from 2 to 6 weeks, whereas regimens containing 5FU have been given more frequently ranging from weekly to three weekly injections.^{8,27,29–31} However, a recent systematic review suggests that

Table 4. Summary of adverse effects

Adverse Effect	Treatment Group ^a		
	TAC	5FU	T + F
Telangiectasia	3	0	1
Skin atrophy	4	0	2
Skin ulceration	0	9	4
Systemic adverse effects	0	0	0

^aValues denote number of patients.

there is no clear correlation of interval with outcome.²⁷ We chose an interval of 3 weeks to account for all three regimens.

With respect to the inclusion criteria, we chose to include only one keloid per patient to allow us to compare systemic adverse effects and a size of 1 to 10 cm was chosen for uniformity and, presumably, a better comparison.

Various methods of achieving pain relief at the site of injection have been described viz. lignocaine as a separate injection or mixed in the same injection. In our view, diluting the drug would require more volume for the same active dose. Our argument against the former is that the separate injection increases the volume of injectate causing more stretch and more pain, and theoretically causes blanching with a smaller active dose. These could compromise on outcome and comparison and, hence, for the sake of our study, drugs were used in their undiluted form without anesthetic injection.

In this study, pain at the site of injection was a common problem with regimens containing 5FU, which is consistent with other studies.^{8,26,29,32} Pain seemed to be blunted by the addition of TAC to 5FU. Oral analgesics alone were given to all patients in the study. Although not included in assessment, feedback from patients revealed that the injection, although painful, was tolerable, short lived, and relieved by oral analgesics alone. Tattooing of 5F, and topical TAC following ablative radiofrequency and ablative laser have been described as alternatives.^{33,34}

The combination regimen has been proven to be better than TAC alone.^{12,35,36} A recent meta-analysis by Ren *et al.* concluded that TAC +5FU is safer and more efficacious than TAC alone.³⁷ Studies have also shown the effectiveness of the combination to be significantly better than 5FU.^{31,38} However, all these studies cannot be directly compared to each other due to lack of standardization. We have attempted standardizing the comparison by using an accepted scar assessment scale. Even so, these objective parameters are observer dependent and prone to errors. Evaluation by the same trained independent observers, such as in our study, can help minimize this error. We also added a dimension of subjective assessment since keloids are ultimately more of a subjective concern for the patient.

In our study, although each regimen was more effective in one parameter than the other, the combination fared better overall, which is in line with the aforementioned studies. A lower number of adverse effects was observed when drugs were

KEY FINDINGS

- Triamcinolone acetonide (TAC), 5-fluorouracil (5FU), and their combination are all effective in keloid scars.
- A combination of TAC +5FU seems to offer the balanced benefit of faster and more efficacious response with lesser adverse effects when compared to individual drugs.
- Treatment has to be individualized and can be combined with one or more modalities to aim for better efficacy and safety.

used as a combination. No systemic adverse effects of 5FU were noted in the study.

A limitation of this study is the short duration of follow-up. All patients in our study were observed for 30 weeks, during which there was no recurrence. A long-term follow-up in such a prospective study is difficult. Our interaction with such patients leads us to believe that this is probably because the patient is unwilling to return when he is convinced that his “disease” has been apparently “cured.” Perhaps a longer prospective study focusing on recurrence might prove more useful in this regard.

Few authors have also suggested combining 5FU and/or TAC with other modalities like surgery, botulinum toxin, and pulsed-dye laser for better outcomes.^{30,39,40} A permanent cure for keloids remains elusive and such studies can help pave the way to achieve it.

CONCLUSIONS

TAC, 5FU, and their combination are all effective in keloid scars. A combination of TAC +5FU seems to offer the balanced benefit of faster and more efficacious response with lesser adverse effects when compared to individual drugs. Treatment has to be individualized and can be combined with one or more modalities to aim for better efficacy and safety.

INNOVATION

Treatment of keloids is a matter of much research. None of the available and newer modalities offer a permanent solution. TAC serves as the current gold standard. Our study provides evidence that TAC improves outcome, both subjective and objective, even when combined with a nonrelated drug like 5-fluorouracil.

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the

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ABOUT THE AUTHORS

Sunil Srivastava, MCh, is presently serving as a Senior Professor in the Department of Plastic Surgery, Sawai Man Singh Medical College and Hospital, Jaipur. His topics of interest include aesthetic and reconstructive surgery. **Aditya Nanasaheb Patil, MS**, is a third-year Resident in the Department of Plastic Surgery, Sawai Man Singh Medical College and Hospital, Jaipur, and

is involved in a number of research activities, and has a keen interest in aesthetic surgery. **Chaitra Prakash, MD, DNB**, is presently serving as a Senior Resident in the Department of Dermatology, Sawai Man Singh Medical College and Hospital, Jaipur. She specializes in Aesthetic Medicine and a number of her research is focused on the same. **Hiranmayi Kumari, MS**, is a second-year Resident in the Department of Plastic Surgery, Sawai Man Singh Medical College and Hospital, Jaipur, and is involved in various research activities, including burn surgeries and aesthetic and reconstructive procedures.

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Abbreviations and Acronyms

5FU = 5-fluorouracil
TAC = Triamcinolone acetonide
TFG = transforming growth factor
VSS = Vancouver Scar Scale