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Comparison of efficacy and safety of intralesional triamcinolone and combination of triamcinolone with 5-fluorouracil in the treatment of keloids and hypertrophic scars: Randomised control trial☆

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ABSTRACT

The treatment of keloid and hypertrophic scar is challenging with no universally accepted mode for permanent ablation. Conventional therapies yield unpredictable results, significant complications and require elaborate hardware.

Objective: The objective was to establish the safety and efficacy of intralesional 5-fluorouracil (5-FU) for the treatment of keloids and hypertrophic scars.

Study design: Randomized controlled trial (RCT).

Place and duration: It was conducted at the Jinnah Burn and Reconstructive Surgery Center/ Allama Iqbal Medical College, Lahore, Pakistan from May 2012 to March 2013.

Subjects and methods: We included 120 patients divided in two groups. The group A patients received intralesional triamcinolone acetonide (TAC) and the group B patients received both 5-FU and TAC. 8 injections at a week interval were given and patients were evaluated at the start of treatment and then at 4th and at 8th week during the treatment and then 4 weeks after the end of treatment. Patents were assessed for mean reduction in scar height, efficacy and complications.

Results: Total of 108 patients completed the study. The mean reduction in the scar height in group B (5-FU+TAC) 1.144+.4717 was markedly better than that of group A (TAC alone) 1.894 +1.0751 (t=4.781, p=.000). The efficacy (defined previously as >50% reduction in initial scar height) was superior in group B 44 (77.2%) than that of group A 25 (49.0% (X2=9.260, p=.002). Recurrence was seen in 39.2% (20) of patients of the group A while in only 17.5% (10) of the cases of group B (P=0.012). Mean follow up was of 22 months.

Conclusion: 5-FU+TAC is safe, easy to administer and effective treatment for problematic scars and has the lower rate of recurrence on larger follow up.

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1. Introduction

Keloids and hypertrophic scars are common benign disorder [1,2]. They result from burns, trauma, surgery, infections like acne and folliculitis [3]. These scars are mainly consist of abnormal deposits of collagen in the scar tissue and result in the significant clinical problem like pain, itching and a deformed look [1,4].

These lesions have the high incidence in darker skin individuals, but the exact figure is different in different studies and ranges from 4.5% to 16% [5,6]. Although some genetic and environmental factors may involve, but exact etiology is still not understood [3].

Although the pathogenesis for these scars is still not understood, but there is some association of scar tissue fibroblasts, which thought to produce an increased amount of collagen [7,8]. So the treatment targeting these fibroblasts may be an essential approach to this abnormal tissue response [8]. Increased vascularity has also been found in these conditions [9].

Although Keloids and hypertrophic scars are morphologically and immunohistochemically different entities and different treatment modalities were suggested in different studies [10–12], still the role of intralesional corticosteroid is advocated in different studies. It improves hypertrophic scars without contractures and inhibit the active fibroblasts. Its role in keloids is described as monotherapy, in combination with surgery [13] or as multimodal therapy [14,15].

Despite being in lime light, there is still no single treatment with predictable outcome. The traditional treatments usually results in recurrence [16]. Although the modern scar treatments claim good results, but still needs to be proven by good quality clinical trials [5]. In addition, the side effects of conventional treatment, i.e. steroid injections are common and significant [17]. In this scenario the ideal treatment should lesser side effects, low cost and does not require any hardware for administration [5].

The use of antineoplastic agents as a treatment option is logical; because these abnormal tissue is in hypermetabolic state [18]. 5-FU has known to affect the fibroblast proliferation in tissue cultures due to its antimetabolite activity [1]. For therapeutic use in these scars a small amount of TAC is added which only reduces the local complications that may occur due to use of pure 5-FU injection [5]. Intralesional 5-FU is however, safe and does not have systemic toxicity as compared to its intravenous use [19].

Rationale of conducting this study is to improve the level of evidence and to establish the safety and efficacy of combined intralesional 5-FU+TAC for keloids and hypertrophic scars [20,21].

2. Material and methods

After approval from the hospital ethical committee, this double-blind, parallel-group, randomized clinical trial was conducted at the Jinnah Burn and Reconstructive Surgery Centre, Lahore from May 2012 to March 2013 with patient recruitment in the first six months. A total of 120 patients with age more than 12 years and with scar size more than 10 mm were included in the study. Patients who took scar treatment in the last 6 months, had any history of renal disease or had altered liver enzymes or white blood cell count were excludedfrom the study. Females of child bearing age were selected after counseling and ruling out pregnancy and breast feeding. An informed consent was obtained from them. Randomization of the patients was done by simple randomization in to two groups. The holder of allocation schedule was off-site. A computer-generated table of random numbers was used for allocation [22] (ratio 1:1); the group A consisted of patients getting intralesional Triamcinolone (TAC) alone and group B consisted of patients getting intralesional 5-FU and TAC.

The sample size of 120 cases; 60 cases in each group was calculated with 80% power of test, 5% level of significance and taking the expected percentage of skin atrophy i.e. 10% in TAC and 0% in 5-FU+TAC group [1] (least among all) in patients with keloid and hypertrophic scars.

Before initiation of treatment all the patients were photographed. The baseline assessment was done and data was entered in proforma. Treatment was administered by an investigator who was blinded for the injection. In each group, 1% xylocaine was injected just deep to the lesion by entering through the edge of the lesion and not through the normal skin to prevent secondary keloid formation. In group A patients once weekly intralesional TAC was given at dose of 10 mg. While in group B, patients were treated with once weekly intralesional injection of 5-FU 45 mg which was mixed with TAC 4 mg. Total 8 injections were given at weekly interval in each group. A trained theater assistant prepared all the Injecting solution.

The therapeutic solution was injected using a 1cc syringe with premounted 27G needle, until slight blanching was observed. The maximum dose given in one session was not more than 2 ml. The injection was given on indurated area of the lesion. Some lesions required multiple pricks separated by approximately 1 cm.

The lesions were assessed by the second researcher at 4 and 8 weeks of treatment and then 4 weeks after completion of the treatment. The parameters noted were mean reduction in scar height, efficacy and complications. The scars were assessed by five points patient and observer scar assessment scale with 0 being no improvement (no reduction is scar height), 1 being poor (0–25% reduction in scar height), 2 being fair (25–50% reduction), 3 being Good (50–75% reduction) and 4 being excellent (75–100% reduction) [8]. Recurrence (new tissue growth at treatment site) [23] was noted at follow up. Data was entered in the proforma.

Efficacy was considered as more than 50% reduction in initial keloids or hypertrophic scars height 4 weeks after the end of treatment [1]. The collected information from the proforma was entered into S.P.S.S. version 11. For Statistical analysis chi-square test was performed to compare the efficacy and complications in both groups.

3. Results

A total of 108 patients completed the study and were analyzed for the outcome, (Table 1), out of whom 51 patients were of group A while 57 patients were of group B. Eight patients lost

Table 1 – Mean reduction of scar height baseline and at 12th week.

Group statistics n=108

	Group of the patient	N	Mean	Std. deviation	t Test P value
Height at start of treatment	TAC alone	51	3.547	.8730	t=−.834
	TAC+5-FU	57	3.665	.5777	P=.406
Height at week 12	TAC alone	51	1.894	1.0751	t=4.781
	TAC+5-FU	57	1.144	.4717	P=.000

follow up and 6 of them were from group A. Four patients discontinued treatment in which 2 patients (group A) due to no significant improvement, 1 patient (group A) due to frequent visits and 1 patient (group B) due to skin ulceration. The mean Age in group A was 31.22+12.559, while the mean age in group B were 27.67+9.480. Male to female ratio was 1:1.318 in group A and 1:1.375. Most of the scars resulted from trauma, piercing or burn and were present mostly at pre-sternal or head and neck areas especially ears.

The mean reduction in the scar height in group B (5-FU+TAC) 1.144+.4717 was markedly better than that of group A (TAC alone) 1.894+1.0751 (t=4.781, p=.000) (Table 1). The efficacy (defined previously as >50% reduction in initial scar height) was superior in group B 44 (77.2%) than that of group A 25 (49.0% (X^2=9.260, p=.002) (Table 2).

Efficacy was compared in Keloid and hypertrophic scars. In keloid scars treatment was efficacious 25 (78.1%) cases in group B than group A 15 (44.1%) cases only and was statistically significant (X^2=7.985, p=.005). In hypertrophic scars treatment was efficacious 27 (76.0%) cases in group B than group A i.e. 10 (58.8%) cases only, (X^2=1.397, p=.003) and no statistical significance was found (Table 3). Patient assessment scale was evaluated at 12th week, 47 (82.5%) cases in group B and 29 (56.9%) cases in group A had good to excellent response. (X^2=11.349, p=.010). Observer assessment scale was evaluated at 12th week, 44 (77.2%) in group B and 26 (51.0%) in group A had good to excellent response. (X^2=12.139, p=.007) (Table 4).

Regarding complication the recurrence rate, after mean follow up of 22 months, was higher in the group A than in group B (39.2% vs. 17.5%). The mean time of recurrence was 10 months (range 2–18 months). The difference in recurrence was statistically significant (P=.012). The overall complication rate in the group A was 35.2% (n=18), which included skin atrophy (17.6%), telangiectasia (23.5%) and hypopigmentation (19.6%). While in group B it was only in 14.0% (n=8) of patients which included skin ulceration (8.8%), hyperpigmentation (5.3%) and telangiectasia (3.5%). (P<.05). Some cases had more than one complication (Table 5).

Table 2 – Comparison of efficacy between treatment groups.

Efficacy	Group A TAC alone	Group B TAC +5-FU	Total	Chi-square value
Yes	25	44	69	X^2=9.260
	49.0%	77.2%	63.9%	P=.002
No	26	13	39	
	51.0%	22.8%	36.1%	
Total	51	57	108	
	100.0%	100.0%	100.0%	

4. Representative cases

4.1. *Group B*

Case — I

This 20 years old female had post-chicken pox sternal keloid for last 12 years (Fig. 1). She had marked improvement in symptoms and appearance at the end of treatment (Fig. 2) and the scar was even better looking at 18 months of follow-up (Fig. 3).

Case — II

This 22 years old female had post burn hypertrophic scarring left cheek for one year (Fig. 4). She had marked reduction in scar height at the end of treatment (Fig. 5) and had even better appearance at 15 months of follow up (Fig. 6).

5. Discussion

These problematic scars are sequelae of abnormal healing in skin and are a significant burden on the health care system and functional and psychological wellbeing of an individual. Although there are plenty of treatment options, but still there is a frustrating number of treatment failures and recurrences. This reflects the need for an effective treatment protocol.

The traditional treatment by steroid injections has shown varying results. Among the corticosteroids, TAC is most commonly used. The dose and treatment interval is variable ranging from 10 to 40 mg/ml which is given between 2 weeks to 4

Table 3 – Comparison of efficacy between keloid and hypertrophic scars treatment groups.

Type of scar	Efficacy	Groups		Total	Chi-square value
		TAC alone	TAC +5-FU		
Keloid	Yes	15	25	40	X^2=7.985
		44.1%	78.1%	60.6%	P=.005
	No	19	7	26	
		55.9%	21.9%	39.4%	
	Total	34	32	66	
		100.0%	100.0%	100.0%	
Hypertrophic scar	Yes	10	19	29	X^2=1.397
		58.8%	76.0%	69.0%	P=.237
	No	7	6	13	
		41.2%	24.0%	31.0%	
	Total	17	25	42	
		100.0%	100.0%	100.0%	

Table 4 – Comparison of Patient and Observer assessment scale between treatment groups.

	Groups	No improvement	Poor	Fair	Good to excellent (>50%)	
Patient assessment scale	TAC alone	2	4	16	29	X^2=11.349
		3.9%	7.8%	31.4%	56.9%	P=.010
	TAC+5-FU	0	0	10	47	
		0.0%	0.0%	17.5%	82.5%	
Observer assessment scale	TAC alone	2	5	18	26	X^2=12.139
		3.9%	9.8%	35.3%	51.0%	P=.007
	TAC+5-FU	0	0	13	44	
		0.0%	0.0%	22.8%	77.2%	

Table 5 – Comparison of complications between treatment groups.

Complication	Group of the patient				P value
	TAC alone (n=51)		TAC+5-FU (n=57)		
	Frequency	Percentage	Frequency	Percentage	
Skin atrophy	9	17.6%	0	0.0%	.001
Telangiectasia's	12	23.5%	2	3.5%	.002
Hypopigmentation	10	19.6%	0	0.0%	.000
Ulceration	0	0.0%	5	8.8%	.030
Hyperpigmentation	0	0.0%	3	5.3%	.097
Reoccurrence	20	39.2%	10	17.5%	.012

weeks interval. The success rate is 50-100% in different studies [24]. The adverse outcomes like skin atrophy, pigmentation, telangiectasias are unacceptable by some patients [25,26].

With these unpredictable results and significant complications, investigators tried to find an ideal treatment. As these scars have been shown to be in hypermetabolic states [18], the use of antimetabolite as treatment option is logical. It is clear from the histological studies that fibroblasts are the cells which are hyperactive and lay down excessive collagen. Regression of these fibroblasts is dose and time dependent [27].

5-FU has antimetabolite activity which inhibits fibroblasts. When injected intralesionally one or two weekly, it resulted in reduction of fibroblasts activity in these scars [8,28,29]. It is safe when used intralesionally and the systemic effects was not seen with subcutaneous use [19]. The unwanted effects like redness and ulceration is associated with the use of pure 5-FU [5]. So to minimize the adverse effects a small amount of TAC is used, this small amount of TAC is not expected to have any efficacy [5,30]. In this study we took 45mg of 5-FU which is 0.9ml and mixed 4mg TAC which is 0.1ml. This combination is effective with quicker clinical response and with few adverse effects (Fig. A1) [1,28].

This combination was first described by Fitzpatrick [28]. He reported his 9-year experience of administering more than 5000 injections of 5-FU+TAC to over 1000 patients. He added TAC with 5-FU and found that this combination is effective with less pain of administration. He injected 5–10 times depending on the response. But he did not compare his results with traditional treatment.

George Kontochristopoulos et al. published a study from Greece in 2005 [31]. The total number of cases was twenty. 85% of the patients showed more than 50% improvement in scars. The failure rate was 45% with recurrence. Adverse effects like

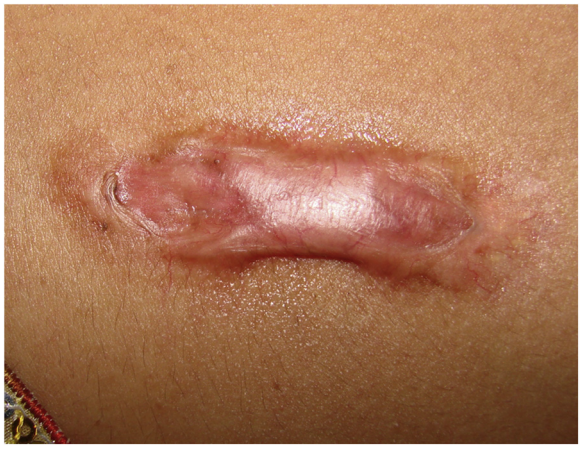

Fig. 1 – Before treatment.

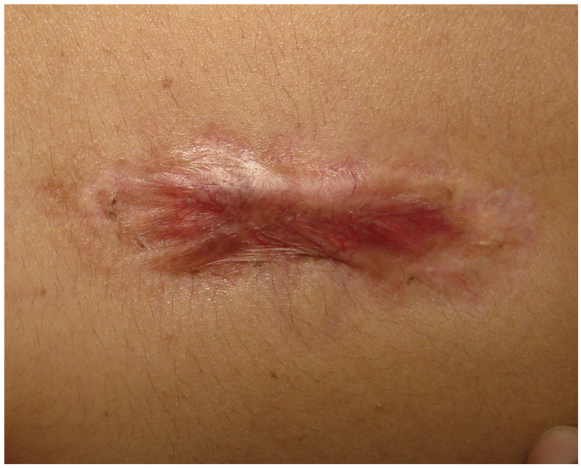

Fig. 2 – At the end of treatment.

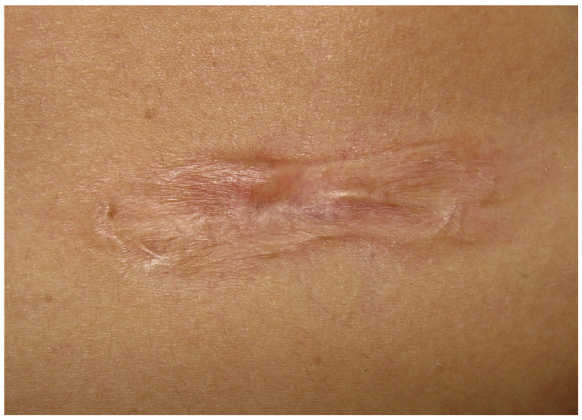

Fig. 3 – At 18 months of follow up.

skin ulceration were seen in 30% of their cases. This study has limited number of cases with no control group.

Darougheh et al. [1] compared the combination of 5-FU and TAC and compared it with patients who had TAC alone. The success rate was 20% in patients of the TAC group and 55% in patients who has combination treatment at 12 weeks follow up. The results in both treatment groups showed improvement but the follow-up was not long.

Although in our study the observer assessment scar scale improvement was 51.0% in the TAC group. The adverse sequelae were seen in 35.2% and recurrence in 39.2% of our study patients at 22 months of mean follow up, which is high and unacceptable for the patients. Manuskiatti and Fitzpatrick [8] showed similar results with intralesional TAC.

The results of the 5-FU+TAC group in our study are comparable with previous studies [27,28]. Nanda and Reddy showed that 80% of the cases have more than 50% improvement [24]. In our study, >50% scar reduction was seen in 77.2% of the cases. In terms of complications, ulceration was seen in only 8.8% of patients, especially in patients with ear keloids, firm to hard scars, and with superficial infiltration, while hyperpigmentation and telangiectasias were seen in 5.3% and 3.5% of the cases respectively. The recurrence rate was 17.5% at 22 months of mean follow up. In different studies, 50–94% of recurrences were seen during one year post treatment [23,32–35]. In our study, the mean time of recurrence was 10 months (range 2–18 months).

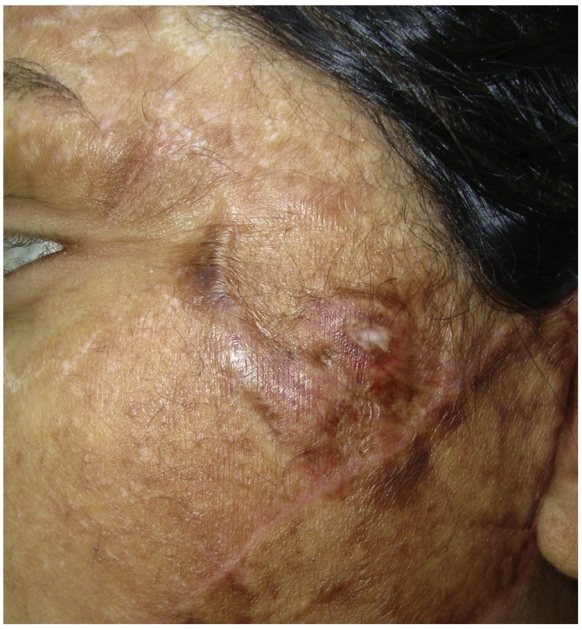

Fig. 5 – At the end of treatment.

A recent meta-analysis of different RCT's [1,8,36,37] showed that intralesional 5-FU and TAC has better response in terms of scar height reduction than the TAC alone [38]. A study by Khan et al. [37] showed good to excellent response in 84% of 5-FU+TAC group while 68% response in TAC alone. This study had short follow up so they did not comment on the recurrence rate. The frequency of complications were also not mentioned individually in each group, only the overall complications were mentioned.

These results show statistical significance ($P < .05$) as well and show that combination therapy has fewer unwanted effects than corticosteroids alone. Blood cell lines can be disturbed by the systemic use of 5-FU, but at the conclusion of

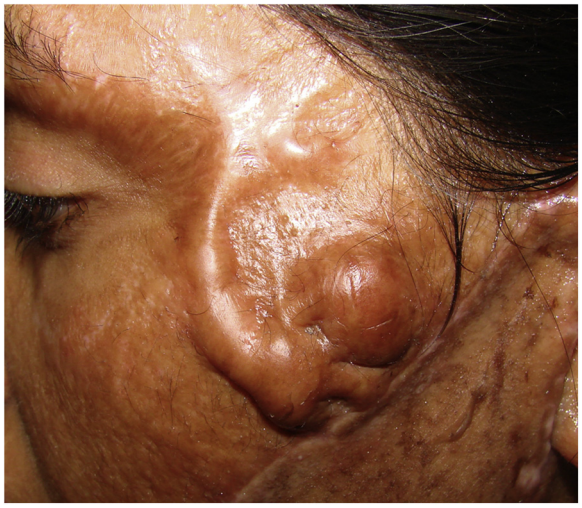

Fig. 4 – Before treatment.

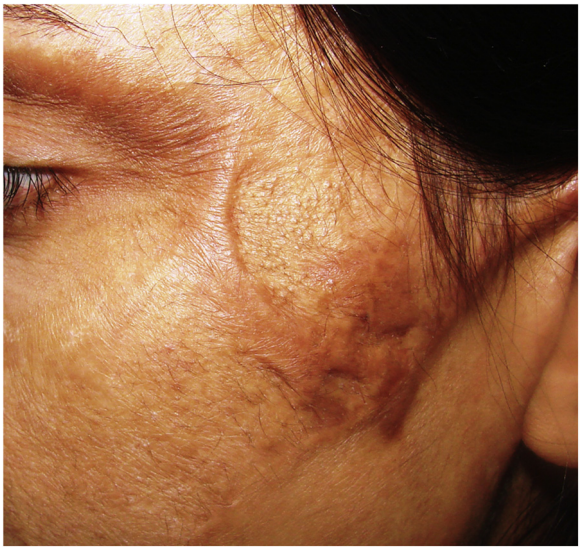

Fig. 6 – At 15 months of follow up.

our study there were no such serious side effects. Even though the intralesional dose did not exceed the recommended dose of 5-FU at each injection session, the use of higher doses has been reported as safe in the literature [28,29].

6. Conclusion

Our study has clearly shown that combination of 5FU with TAC is significantly better in reducing the symptoms and appearance of these scars and has longer lasting results compared to steroid alone.

Trial registry

The Trial is registered with Australian New Zealand Trial Registry www.anzctr.org.au.

The trail Number is ACTRN12612000546853.

Conflict of interest

This is to inform that we (authors) have read the current "Guide for Authors". Authors have no financial and personal relationships with any other people or organizations that could inappropriately influence (bias) this work.

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Appendix A.

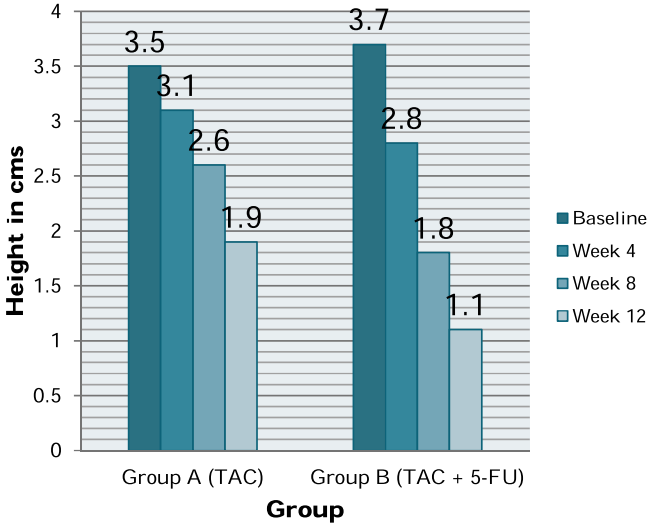

Fig. A1 – Mean reduction in scar height (n=108).

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