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A COMPARATIVE STUDY OF INTRALESIONAL TRIAMCINOLONE ACETONIDE ALONE VERSUS COMBINATION OF 5-FLUOROURACIL AND TRIAMCINOLONE ACETONIDE IN THE TREATMENT OF KELOID

Dermatology

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ABSTRACT

Background: Keloids are benign proliferative condition of dermal fibroblast. Intralesional corticosteroid improves keloid but associated with significant adverse effects like dyspigmentation, tissue atrophy and telengectasia and contraindicated in certain conditions like hypertension and diabetes. 5-Fluorouracil (5-FU), a pyrimidine analogue with an inhibitory effect on TGF-β induced fibroblast proliferation is useful in treatment of keloids but is associated with ulceration and pain. A low dose of Triamcinolone if added to 5-FU injection overcomes these issues.

Approach: This study was conducted in a tertiary care hospital. Sixty patients; thirty in each group were included. In group A, once weekly intralesional Triamcinolone and in group B, intralesional injection of Triamcinolone mixed with 5-Flurouracil in 1: 9 dilution were injected for 8 sessions. Parameters of Vancouver scale were noted at the baseline and at the end of treatment.

Results: Out of 60 patients enrolled in this study. The combination group was better in improving height (62.11% vs 78%), pliability (44.14% vs 8.81%), and vascularity (55.78% vs 61.30%) and results were statistically significant (P valve <0.05) however it was not better in improving pigmentation (43.47% vs 20%) and volume (69.79% vs 80.76%) (P valve > 0.05). Pain and pruritus improved completely (100%) in both the groups at the end of the treatment. Excellent improvement in patient and observer assessment score was seen in 96.67% vs 3.33% in combination group and TAC group respectively. The difference was statistically significant (P valve<0.05). Combination was better irrespective of age of the patient, duration, site, and origin of keloid. All patients treated with 5 FU develop ulceration and pain.

Conclusion: Both the therapies are effective but combination is superior to TAC alone. We advocate that 5-FU should be used alone, addition of TCA does not have any added advantage in therapeutic outcome rather it increases the cost of treatment.

KEYWORDS

Keloid, Intralesional triamcinolone acetonide, Intralesional 5-fluorouracil

INTRODUCTION:

Keloids are benign proliferative condition of dermal fibroblasts[1] Common sites are earlobe, shoulders, upper trunk and legs.[2] Patients often present with itching, tenderness, pain, dysesthesia, restriction of movement and cosmetic disfigurement.[1][3] It may be spontaneous in origin or may be secondary to burn, infection, physical or chemical trauma, and inflammatory conditions such as acne.[2]

A wide range of therapies exist with discordant results including intralesional steroid injection, surgical excision, cryotherapy, laser therapy, application of silicone gel sheets, imiquimod, 5- fluorouracil (5-FU), bleomycin, retinoid, and interferon-alpha2b.[4] Intralesional corticosteroids improve keloid but they are associated with significant adverse effects such as hypopigmentation, tissue atrophy and telengectasia in and around the lesion.[5] 5-Fluorouracil (5-FU), a pyrimidine analogue with anti-metabolite activity has an inhibitory effect on TGF-β induced expression of the type I collagen gene so inhibit fibroblast proliferation.[6][7] However local complications related to 5 FU limits the therapeutic use; to overcome these complications a low dose of Triamcinolone is to be added to 5-FU injection. [7]

Therefore, this study is aimed to compare the efficacy of intralesional Triamcinolone Acetonide versus combination of intralesional 5-Fluorouracil with low dose of Triamcinolone Acetonide in treatment of keloid.

AIMS AND OBJECTIVES:

Aim: To compare the efficacy of intralesional Triamcinolone Acetonide alone versus combination of intralesional 5-Fluorouracil with low dose of Triamcinolone Acetonide, in the treatment of keloid.

OBJECTIVES:

1. Primary objective is to evaluate the efficacy of Intralesional Triamcinolone Acetonide and intralesional 5-Fluorouracil combined with reduced dose of Triamcinolone Acetonide in Keloid and compare the same in terms of Vancouver scar scale (VSS) and three point scale.
2. Secondary objective is to note the side effects of intralesional Triamcinolone Acetonide and 5-Fluorouracil & compare the same.

MATERIAL & METHODS:

Written informed consent was obtained from all the patients. Ethical clearance was obtained from the institutional research review board (353-/MC/EC/2020). Study was conducted over a period of 12 months (May 2019 to April 2020) in the department of Dermatology. This was an OPD based self financed project.

Sixty patientswho had Keloid, diagnosed by clinical features; aged >12 years and size (length) of the scar ≥20mm were included in the study. Patients who took treatment for Keloid in past 6 months, had history of any liver or kidney disease/deranged liver function or renal function tests, active infection in body, pregnant or lactating females, HIV or Hepetitis B positive were excluded.

The socio-demographic parameters, detailed history and clinical examination was done and recorded in predesigned proforma. Patients were randomized in two groups; 30 each by Odd-Even method. Only single lesion was treated in each patient. In Group A, all patients were

treated with once weekly intralesional Triamcinolone Acetonide 40 mg/ml (0.1 ml to be injected at 1cm distance) for a total of 8 sessions while in Group B, patients were treated once weekly with intralesional injection of Triamcinolone Acetonide 4 mg (0.1 mL of 40 mg / mL TAC) mixed with 5-Flurouracil 45 mg (0.9 mL of 50 mg/mL 5-FU) for a total of 8 sessions. The solution was injected into the body of the keloid using 28G needle until slight blanching was visible. The maximum volume of injection per cm^2 did not exceed 0.5 mL. Photographs of lesion were taken at enrolment and on subsequent visits for assessment.

Assessment and analysis

To assess the clinical response photographs were taken at the beginning and at the end of treatment. Clinically assessment was done by the parameters of Vancouver scale (height, volume, pliability, vascularity, pigmentation, pain and pruritus) and were noted at i.e. 8^{th} week and after one month of followup i.e. 12^{th} week.

Length, width and height were measured with a dial caliper and pigmentation, vascularity and pliability were assessment by Vancouver Scar Scale (VSS). Pain and pruritus were measured by three point scale; 0: no pain/pruritus, 1: occasional pain/pruritus (not required any treatment), 2: severe pain/ pruritus requiring treatment.

Patient self-assessment and observer assessment by a scar assessment scale was done according to reduction in height after therapy; 0: no improvement (no reduction), 1: poor (0–25% reduction), 2: fair (25–50% reduction), 3: Good (50–75% reduction), 4: excellent (75–100% reduction).

The lesion was assessed by the second researcher at 1^{st} visit and then at 12^{th} week for any recurrence. The parameters noted were mean reduction in scar height, efficacy and complications. Any recurrence was noted after one month of follow up.

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data were presented as numbers (percentage and proportion) and were compared among groups using Chi square test. The quantitative data were presented as mean and standard deviation and were compared by unpaired students t-test and ANOVA test. Probability was considered to be significant if P value was less than 0.05.

RESULTS:

In present study, sixty patients were included matched by age and sex, thirty in each group with mean age of presentation being 34.63±19.09 and 32.30±17.49 in TAC alone and combination group respectively. Forty one (68.33%) patients were males (70% vs 66.66% in TAC vs Combination group respectively) and 19 (31.66%) patients were females (30% vs 33.34%) in TAC vs Combination group respectively) with a male: female ratio of 2.5:1 (2.3:1 vs 2:1 in TAC vs Combination group respectively). Baseline parameters were comparable between two groups. [Table 1]

Table 1: Demographic profile and base line parameters

	TAC (N=30)		TAC + 5 FU (N=30)		Result (P value)
	Mean	SD	Mean	SD	
Age (mean ± SD), (years)	34.63	19.09	32.30	17.49	0.623
Sex, Number (%) Female Male	9 (30) 21 (70)		10 (33.34) 20 (66.66)		1.00
Height (mm)	2.32	0.90	2.57	1.43	0.420
Volume (mm^3)	1676.33	2438.19	2221.50	2318.67	0.378
Pliability	3.27	0.83	3.33	0.84	0.758
Vascularity	1.97	0.85	1.90	0.71	0.743
Pigmentation	1.70	0.60	1.57	0.68	0.422
Pain	0.77	0.82	0.57	0.68	0.306
Pruritus	0.80	0.76	0.87	0.63	0.712

On comparison of two groups(on the basis of Vancouver scale) we observed significant reduction in height (72.41% vs 87.15%), pliability (50.15% vs 63.06%) and vascularity (64.46% vs 73.68%) in both the groups, triamcinolone alone vs combination respectively. However, the reduction was significantly greater in combination group (P value <0.05).

The other parameters involving pigmentation (47.05% vs 49.04%) and volume (72.99% vs 86.74%) were decreased in both the groups; triamcinolone alone vs combination respectively, without being significant differences in both the groups (P value >0.05).Pain and pruritus was subsided completely in both the groups without any significant difference.[Table 2]

Table 2: Comparison of Vancouver scale parameter between Group A & B at the end of the 8 weeks after treatment and one month (12th weeks) of follow up.

	TAC (N=30)		TAC + 5 FU (N=30)		Result (P value)
	Mean	SD	Mean	SD	
Height (baseline)	2.32	0.90	2.57	1.43	0.420
8 week	**0.64**	**0.58**	**0.33**	**0.55**	**0.036**
12 week	**0.64**	**0.58**	**0.33**	**0.55**	**0.036**
P value	**<0.001**		**<0.001**		
Volume (baseline)	1676.33	2438.19	2221.50	2318.67	0.378
8 week	452.61	790.09	294.44	578.67	0.380
12 week	452.61	790.09	294.44	578.67	0.380
P value	**<0.05**		**<0.001**		
Pliability (baseline)	3.27	0.83	3.33	0.84	0.758
8 week	**1.63**	**0.66**	**1.23**	**0.43**	**0.049**
12 week	**1.63**	**0.66**	**1.23**	**0.43**	**0.049**
P value	**<0.05**		**<0.001**		
Vascularity (baseline)	1.97	0.85	1.90	0.71	0.743
8 week	**0.73**	**0.53**	**0.50**	**0.51**	**<0.05**
12 week	**0.73**	**0.53**	**0.50**	**0.51**	**<0.05**
P value	**<0.001**		**<0.001**		
Pigmentation (baseline)	1.70	0.60	1.57	0.68	0.422
8 week	0.90	0.40	0.80	1.00	0.612
12 week	0.90	0.40	0.80	1.00	0.612
P value	**<0.001**		**<0.001**		
Pain (baseline)	0.77	0.82	0.57	0.68	0.306
Final	**0.00**	**0.00**	**0.00**	**0.00**	-
Pruritus (baseline)	0.80	0.76	0.87	0.63	0.712
Final	**0.00**	**0.00**	**0.00**	**0.00**	-

Majority (96.67%) of patients in combination group showed excellent improvement (>75%) in patient and observer score, remaining 3.67% showed good response. In TAC alone group only 6.67% cases showed excellent (>75%) improvement while 3.33%, 46.67% and 43.33% cases showed 50-75% , 25-50% and ≤ 25% good, fair and poor improvement in patient and observer score respectively. Excellent improvement was seen in 96.67% vs 3.33% in combination group and TAC group respectively. The difference was statistically significant (P valve<0.05). Patient self-assessment and observer assessment by a scar assessment scale according to reduction in height after therapy was statistically significant in combination group. (P valve<0.05). [Table 3]

Table 3: Observer and Patient Assessment Score

	TAC (N=30)		TAC + 5 FU (N=30)		Result (P value)
	Mean	SD	Mean	SD	
Observer Assessment score	1.73	0.83	3.97	0.18	p<0.001
Patient Assessment Score	1.73	0.83	3.97	0.18	p<0.001

Chest and upper limb keloids responded better than lower limb keloids with combination group and results were statistically significant. Combination therapy works better in spontaneously originated keloid but no significant difference was seen in keloid originated secondary to trauma or acne. Combination therapy works best in middle age patient with older lesions and all results were statistically significant (P value<0.05). [Table 4]

Table 4: Response to treatment according to different sites, origin, duration, age of the patient.

	TAC (N=30)		TAC + 5 FU (N=30)		Result (P value)
	Mean	SD	Mean	SD	
Site					

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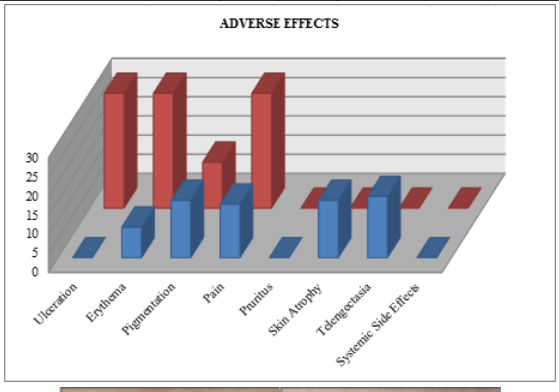
Chest	Height	0.66	0.66	0.22	0.17	0.005
Lower limb	Height	0.5	0.35	1.75	1.76	>0.05
Upper limb	Height	0.7	0.51	0.1	0	<0.05
Origin						
Spontaneous	Height	0.75	0.83	0.22	0.15	0.023
Trauma	Height	1.86	3.34	0.58	1.07	>0.05
Acne	Height	0.32	0.10	0.3	0.28	>0.05
Age group						
15-35 yrs	Height	0.64	0.38	0.25	0.65	0.04
36-55 yrs	Height	1.10	0.90	0.20	0.17	0.03
56-75 yrs	Height	0.36	0.36	0.35	0.17	0.960
Duration of lesion						
<5 yrs.	Height	0.58	0.39	0.39	0.67	0.244
>5 yrs.	Height	0.87	1.09	0.22	0.18	0.036



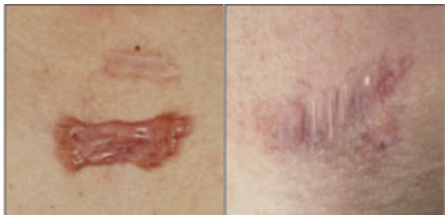


Figure 1A and 1B (Triamcinolone alone group) 1A: At the beginning of the treatment (0 week) 1B: At the end of the treatment (12th week)

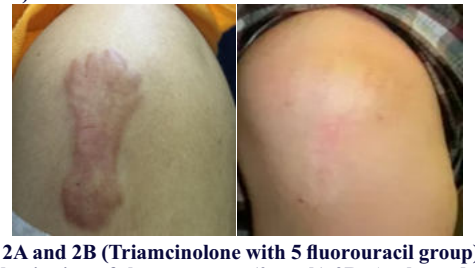


Figure 2A and 2B (Triamcinolone with 5 fluorouracil group) 2A: At the beginning of the treatment (0 week) 2B: At the end of the treatment (12th week)

DISCUSSION

In present study, sixty age and sex matched patients; thirty in each group with mean age of presentation, 34.63±19.09 and 32.30±17.49 years in TAC alone and combination group respectively, with a male: female ratio of 2.5:1 were included. This was as accord with study done by Prabhu A. et al [1] and Khalid FA et al. [7] After 8 weeks of treatment we noted statistically significant decrease in all the parameters of Vancouver scale in both the groups (P value <0.05). The combination group did better in improving height (62.11% vs 78%), pliability (44.14% vs 8.81%), and vascularity (55.78% vs 61.30%) and results were statistically significant (P valve <0.05%) however it was not better in improving pigmentation (43.47% vs 20%) and volume (69.79% vs 80.76%) (P valve > 0.05%). Pain and pruritus improved completely (100%) in both the groups at the end of the treatment.

Majority (96.67%) of patients in combination group showed excellent improvement (>75%) in patients' and observer's score, remaining 3.67% showed good response. In TAC alone group, only 6.67% cases showed excellent (>75%) improvement while 3.33%, 46.67% and 43.33% cases showed good, fair and poor improvement in patients and observer's score respectively. Excellent improvement was seen in 96.67% vs 3.33% in combination group and TAC group respectively. The difference was statistically significant (P valve<0.05).

Fitzpatrick et al[8], Khan et al[9] and Darougheh et al [6] shows similar result with same 1:9 dilution combination but Mutalik and Patwardhan[10] and Davison et al. [11] used 1:1 dilution instead of 1:9 in combination group also got similar results when compared in both the groups. Thus, low dose of corticosteroids recommended and its addition primarily functions to reduce the incidence of unwanted side effects. According to Bayat A et al [12] and Urioste SS et al [13] ear lobe was the most common site of keloid. However, we observed the chest as commonest site in 70% of cases. Chest and upper limb keloids responded better in both the groups, reduction in height was greater in combination group than TAC alone (P valve <0.05). This was similar to study done by Shaheen A et al [14] and Nanda S, Reddy B.S, [2004][15]

According to the duration of keloids, keloids of recent onset (<5 Years) showed greater response in both the groups with greater reduction in height in combination group in comparison to TAC alone which may be due to greater vascularity of lesions and higher chances of remodeling in recent onset keloids. These results were comparable with study done by Nanda et al [15]

Majority of the keloids were spontaneous in origin (41.66%) and responded better to combination. It may be due to absence of underlying pathology and greater vascularity in these keloids. Both the drugs act well in younger population aged <50 years but combination is better with statistically significant difference (P value <0.05). It may be due to lower vascularity and mitotic rate in elderly causing decreased activity of 5 fluorouracil which acts on rapidly dividing cells.[16] According to our knowledge no such study has been done that compares these two dugs according to the age of patient, site, and origin of keloid.

Both the groups in our study were associated with side effects including ulceration, pain, erythema and dyspigmentation seen in 100%, 100%, 100% 40% and 0%, 73.33%, 26.67% & 50% cases respectively in combination and TAC group respectively. Ulceration at the injection site was seen only in combination group in all cases and healed easily with oral and topical antibiotics. Oral analgesics were given for one day for pain in combination group. No systemic side effects following injections were observed in our study which correlated with previous studies done by Prabhu A et al[1] Darougheh A et al.[6] However George Kontoch et al.[17] reported skin ulceration in only 30% of cases contradict to present study that may be due to ethnic and racial difference in study group and small sample size.

Many studies [5][7][9] claimed that addition of small dose of steroid will decrease pain during injection and ulceration due to anti-inflammatory properties of steroid but this is not true with our study as all the cases in combination group experienced severe pain during injection lasting for 24 hours and developed skin ulceration at the injection site.

In our study, although both regimens were effective in treatment of keloids but the combination was overall superior than TAC alone, which is in-line with the aforementioned studies. As claimed in previous studies that adverse effects can de decreased if the 5 FU is used in combination rather alone, however it was not consistent in our study. None of the patient in index study showed any systemic adverse effect which is in concordance with other studies.

CONCLUSIONS:

In conclusion both the therapies are effective but combination is much superior to TAC alone. The Vancouver score is a sensitive parameter to assess the improvement after therapy, at the same time assessment by the patient and an independent observer is also important. In our study both tools were used to assess the response. We advocate that 5-FU should be used alone, addition of very small amount of TCA does not have any added advantage in therapeutic outcome rather it increases the cost of treatment. 5- FU alone can be used in situations like diabetes and hypertension where triamcinolone is contraindicated. The small and medium size lesions respond well in both the groups however in the large lesions combination was better than TAC alone.

Limitations: This study is limited by its small sample size and shorter duration of follow-up after treatment. Long terms follow-up is needed to ascertain the result.

Declaration of patient consent:
The authors certify that they have obtained written informed consent from all the patients. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest - There are no conflicts of interest.

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