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Original Research Article

A Double Blind Comparative Study of Efficacy and Safety of Intra-lesional Triamcinolone Alone versus Intra-lesional 5-Fluorouracil and Triamcinolone Combination in Treatment of Keloids in a Tertiary Care Hospital.

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Abstract:

Introduction: Keloids are benign dermal collagen and fibro-proliferative growths. They are a variant of wound healing and are prone to recur. Though there are a variety of treatment options for keloids, no standardized treatment is available. Intra-lesional steroid is the commonest treatment modality in use. 5-Fluorouracil, a cytotoxic drug in combination with steroid relieves symptoms of keloids. Hence the study was planned.

Objectives: To compare early improvement, efficacy, response and safety of Triamcinolone alone with 5-Fluorouracil and Triamcinolone combination in keloids treatment.

Materials and Methods: An open labelled randomized comparative study was conducted. 60 patients with keloids, were randomly divided into 2 groups of 30 each. Group A patients were given intra-lesional Triamcinolone 1ml (40mg/ml) and Group B patients were given a combination of 5-Fluorouracil 0.9ml (50mg/ml) and Triamcinolone 0.1ml (40mg/ml) intra-lesionally, weekly once for 4 weeks, later fortnightly once for 6 weeks. Follow- up was done till 12 wks. Efficacy was assessed by noting the shrinkage of keloid (volume), improvement in vascularity, pigmentation, pain and itch score. Safety was assessed by adverse effects experienced by the patients. Data was collected, statistical analysis done and results were compiled.

Result: Group B patients showed better improvement than Group A patients in terms of lesion shrinkage (78.69%, 48.72%), vascularity (77.5%, 36.84%), pigmentation (43.75%, 30.3%), itch relief (87.8%,53.09%) & pain relief (87.84%,54.05%). There was statistical significance ($p < 0.002$) between the groups in all parameters except pigmentation. Pain at the injection site was experienced by all patients in both groups (100%) and local burning sensation by 3 patients in Group A (10%) compared to 1 patient (3.33%) in Group B. Hypopigmentation and hyperpigmentation were seen in 3.33% patients in Group A and Group B respectively. Good to excellent response was seen in >50% patients in both the groups except for keloid volume which was fair to good in 75% Group A patients. Response to treatment with regard to all parameters was much better in Group B than in Group A.

Conclusion: Combination of 5-Fluorouracil and Triamcinolone has early onset of action, is more effective and safer than Triamcinolone alone to treat keloids.

Keywords: 5-Fluorouracil, Triamcinolone, Keloids, Efficacy, Safety.

Introduction

Keloids are benign hyperproliferative dermal fibrous and connective tissue growths which occur due to an abnormal response to injury, burns, inflammation or surgery. Rarely they occur spontaneously, do not regress spontaneously but tend to recur even after treatment. They are associated with pain, pruritus, restricted movements at joints, and cosmetic deformities. [1,2] They are common in darker skinned individuals and on the trunk, face, neck and upper limbs. [3]

In normal wound healing, TGFβ (tissue growth factor β) is produced which stimulates fibroblasts to produce collagen and fibronectin - the extracellular matrix and helps to form granulation tissue. After re-epithelialization of the wound, apoptosis plays a role to form normal scar. Whereas in keloids, fibroblast apoptosis doesn't occur so leads to formation of abnormal scar. Also, growth factors like VEGF (vascular endothelial growth factor), cytokines and MMP2 (matrix metalloproteinase-2) play a role in

keloid formation. TGFβ produces angiogenesis in keloids. [4,5,6,7,8,9] Also, cell mitosis inhibition disrupts cell proliferation and induces cell apoptosis. To treat keloids, all these have to be kept in check. So, corticosteroids, 5 Fluorouracil, Mitomycin and Bleomycin are the currently used antimitotic drugs. Clinical effectiveness of local steroid injection is 50%-100%. Triamcinolone (TAC) is the widely used steroid to treat keloids. It inhibits inflammatory cell migration and phagocytosis, decreases VEGF, $TGF\beta_1$, insulin like growth factor, oxygen supply to the wound, fibroblast proliferation, collagen formation and arrests G1phase of cell cycle with no cytotoxic or apoptotic effect. Hence it helps in scar regression. Side effects of Triamcinolone are skin and subcutaneous atrophy, hypopigmentation, telangiectasia, cushingoid features, local skin necrosis and ulcer formation.

5 Fluorouracil (5 FU) is a pyrimidine analogue, an antimetabolite, arrests cell growth at G2 phase, inhibits fibroblast proliferation greatly, inhibits thymidylate synthetase thus blocks RNA and DNA synthesis, is cytotoxic, induces apoptosis of fibroblasts by increasing P53 expression and decreasing P21, decreases collagen, increases MMP2 thus degrades extracellular matrix, decreases VEGF and TGFβ. Intralesional 5 FU is well tolerated, produces minimal serious side effects. Side effects are local erythema, pain, pigmentation, swelling and rarely ulceration. [10,11,12,13]

Combination of TAC and 5FU have reported a significant cell proliferation inhibition, cell death and efficacy, but not a significant downregulation of VEGF and TGFβ. Combination produced less pain at injection site. [10,12] Keeping this in background, we conducted a study to see for the early improvement, efficacy, response and safety of TAC alone with combination of 5FU and TAC in keloids treatment.

Objectives: To compare early improvement, efficacy, response and safety of Triamcinolone alone with 5-Fluorouracil and Triamcinolone combination in keloids treatment.

Materials and Methods

A double blinded, block randomized, comparative, interventional study was conducted by the department of Pharmacology in minor OT of a tertiary care hospital, in association with the department of Surgery, from Jan 2015- Sep 2015; after obtaining Institutional Ethics Committee approval. Thorough examination and required investigations were done, inclusion-exclusion criteria applied and an informed consent was taken from every subject prior to the conduction of procedure by an experienced plastic surgeon. Two groups (Group A and Group B) each had 30 patients having keloids. Group A patients received intra-lesional Triamcinolone 1ml (40mg/ml) and Group B patients received intralesional combination of Triamcinolone 0.1ml (40mg/ml) and 5 Fluorouracil 0.9ml (50mg/ml); weekly once for the first four weeks later fortnightly once for another 6 weeks and were followed up till 12 weeks. Each intralesional injection was given such that a maximum of 0.5ml of drug/ drugs was injected into 1 cm^2 and not more than 2ml was injected per session using a 27G insulin syringe. Each patient was observed for 15 minutes after giving intralesional injection, to see for any immediate side effect due to the drug/drugs. No other drugs like anti-inflammatory or local anaesthetics and other treatment modalities were given simultaneously with this treatment. Assessment was done at each visit. Efficacy of drugs was assessed using VSS score (Vancouver Scar Scale) except pliability. Scar volume was used instead of scar height. Scar volume was measured using calipers, vascularity by visual inspection, pigmentation was scored after blanching the keloid and comparing with the surrounding skin. Subjective scores of pain and itch were given scores from 0-10, as done in POSAS (Patient Observer Scar Assessment Scale) and were assessed by the improvement in their scores. Response to treatment was graded as excellent (76%-100% improvement in scores), good (51%-75%), fair (26%-50%) and poor (≤25%). Adverse effects experienced by patients allowed us to assess the safety profile of both drugs. Data collected was analysed statistically using Jamovi 2.3.28 version. Mean ± SD, percentage and p value were calculated using Wilcoxon Rank test. p value <0.05 was considered as statistically significant.

Inclusion Criteria: Patients with keloid aged 20-60 yrs of either sex, attending Surgery out- patient-department, keloid size <10 cm in any direction. Only one keloid per patient was considered for our study.

Exclusion Criteria: Hypertrophic scars, patients who have taken treatment previously for that keloid, pregnant women, lactating mothers, married women planning to conceive during treatment, patients with diabetes mellitus; hypertension; cancer; liver disease; renal disease; chronic inflammatory disease and patients on immunosuppressants.

Investigations at baseline and at 12 weeks included blood pressure measurement, complete hemogram, random blood sugar, renal and liver function tests.

Results

Out of 60 patients, 32 were females and 28 were males. Mean age was 44±4.6 years in group A and 41±3.8 years in Group B. There was no statistical significance in pre-injection baseline VSS scores, pain and itch scores. Keloid volume in Group A and Group B at baseline was 5.87±4.3 and 5.82±5.4, and at 12 weeks was 3.01±2.0 and 1.24±1.3 respectively. Keloid volume improvement from baseline to end of

study in Group A and Group B was 2.86±2.2 and 4.58±4.1 respectively. Improvements in keloid volume, vascularity, pigmentation, pain and itch were statistically significant within individual groups ($p<0.002$). All parameters were better in Group B compared to Group A and were statistically significant from 10th week except vascularity which was statistically significant from 8th week till the end of study. No statistical significance in pigmentation was seen throughout the study period. Early improvement in all the parameters were seen in Group B compared to Group A except for pigmentation which started at 6th week in both the groups. Early improvement in pain and itch started at 2 weeks in Group B and at week 4 in Group A, keloid volume and vascularity improvement were seen at week 3 in Group B whereas in Group A it was at week 4 and week 6 respectively. (See tables 1,2,3;4 and figures 1,2,3 ,4,5)

Table 1: Vancouver scar scale scores (mean ±SD) in both the groups

Keloid character	Volume (cm3)			Vascularity			Pigmentation		
Group	**A**	**B**	**p value**	**A**	**B**	**p value**	**A**	**B**	**p value**
0 wk	5.87±4.3	5.82±5.4	0.81	1.9±0.7	2±0.9	0.71	1.65±0.6	1.6±0.6	0.77
1 wk	5.87±4.3	5.82±5.4	0.81	1.9±0.7	2±0.9	0.71	1.65±0.6	1.6±0.6	0.77
2 wk	5.87±4.3	5.82±5.4	0.8	1.9±0.7	2±0.9	0.71	1.65±0.6	1.6±0.6	0.77
3 wk	5.87±4.3	5.45±5.1	0.57	1.9±0.7	1.7±1.3	0.54	1.65±0.6	1.6±0.6	0.77
4 wk	5.73±4.2	4.54±4.2	0.26	1.9±0.7	1.5±1.3	0.27	1.65±0.6	1.6±0.6	0.77
6 wk	4.86±3.7	3.71±3.5	0.23	1.8±0.7	1.25±1.2	0.13	1.5±0.8	1.45±0.8	0.93
8 wk	4.2±3.2	2.9±2.8	0.13	1.65±0.8	0.95±1.1	0.04*	1.3±0.8	1.25±0.8	0.89
10 wk	3.47±2.7	2.10±2.1	0.04*	1.5±1	0.65±0.8	0.009*	1.25±0.8	1.1±0.7	0.61
12 wk	3.01±2.0	1.24±1.3	0.002*	1.2±1.01	0.45±0.6	0.023*	1.05±0.8	0.9±0.6	0.61
p value* (0 and 12 wk)	<0.001*	<0.001*		<0.001*	<0.001*		0.002*	<0.001*	

*Wilcoxon Rank test

Table 2: Subjective scale scores (mean ±SD) in both the groups

Keloid character	Pain			Itch		
Group	**A**	**B**	**p value**	**A**	**B**	**p value**
0 wk	3.7±3.1	3.7±3.2	1	4.05±2.8	4.1±3.1	0.96
1 wk	3.7±3.1	3.7±3.2	1	4.05±2.	4.1±3.1	0.96
2 wk	3.7±3.1	3.45±3.0	0.75	4.05±2.8	3.85±3.1	0.81
3 wk	3.7±3.1	3.05±2.7	0.39	4.05±2.8	3.2±2.8	0.43
4 wk	3.4±2.8	2.6±2.2	0.32	3.85±2.5	2.75±2.4	0.22
6 wk	2.95±2.5	2.05±1.7	0.17	3.2±2.4	2.05±1.7	0.12
8 wk	2.5±2.1	1.5±1.3	0.09	2.8±2.1	1.65±1.3	0.06
10 wk	2.15±1.7	0.95±0.9	0.01*	2.4±1.7	1.2±1.01	0.01*
12 wk	1.7±1.4	0.45±0.5	0.003*	1.9±1.4	0.45±0.6	0.003*
p value*(0 wk and 12 wk)	0.001*	0.002*		<0.01*	<0.001*	

*Wilcoxon Rank test

Table 3: Vancouver scar scale scores improvement (mean ±SD) in both the groups

Keloid character	Volume (cm3)		Vascularity		Pigmentation	
Group	**A**	**B**	**A**	**B**	**A**	**B**
0 wk	5.87	5.82	1.9	2	1.65	1.6
2 wk	0	0	0	0	0	0
3 wk	0	0.37±0.3	0	0.3±0.3	0	0
4 wk	0.04±0.0	1.28±1.1	0	0.5±0.4	0	0
6 wk	1.01±0.5	2.11±1.8	0.1±0.01	0.75±0.3	0.15±0.2	0.15±0.2
8 wk	1.67±1.1	2.92±1.8	0.25±0.1	1.05±0.1	0.35±0.1	0.35±0.2
10 wk	2.4±1.5	3.72±3.3	0.4±0.2	1.35±0.2	0.4±0.1	0.5±0.1
12 wk	2.86±2.2	4.58±4.1	0.7±0.2	1.55±0.2	0.5±0.1	0.7±0.1

*Wilcoxon Rank test

Table 4: Subjective scale scores improvement (mean ±SD) in both the groups

Keloid character	Pain		Itch	
Group	**A**	**B**	**A**	**B**
0 wk	3.7	3.7	4.05	4.1
2 wk	0	0.25±0.1	0	0.2±0.1
3 wk	0	0.65±0.5	0	0.85±0.3
4 wk	0.3±0.2	1.1±0.9	0.20±0.2	1.3±0.7
6 wk	0.75±0.5	1.65±1.4	0.85±0.3	2.0±1.4
8 wk	1.2±0.9	2.2±1.8	1.25±0.7	2.4±1.8
10 wk	1.55±1.3	2.75±2.2	1.65±1.1	2.85±2.1
12 wk	2.00±1.6	3.25±2.7	2.15±1.3	3.6±2.5

*Wilcoxon Rank test

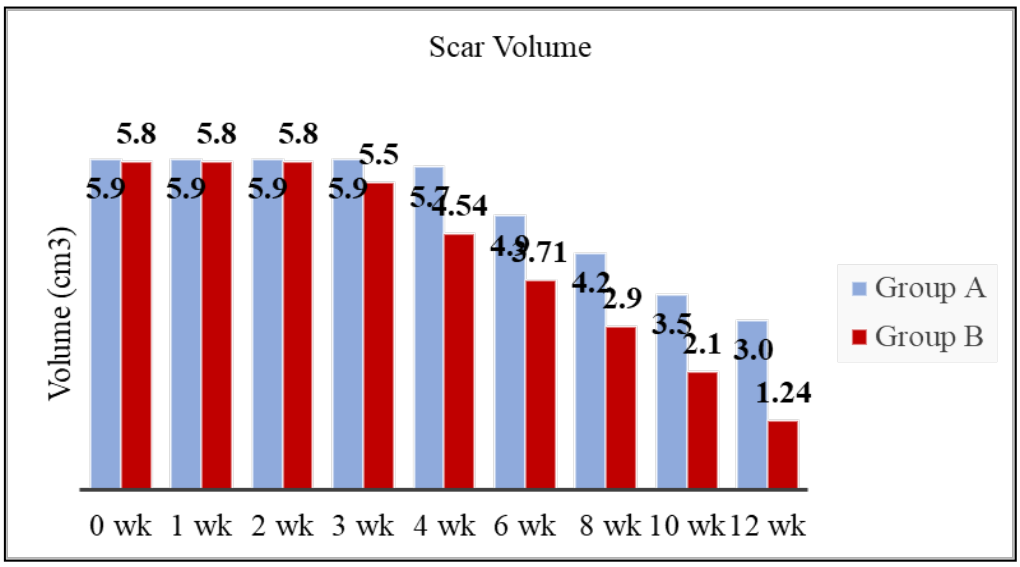

Figure 1: Keloid Volume (cm^3) at different weeks in both the groups

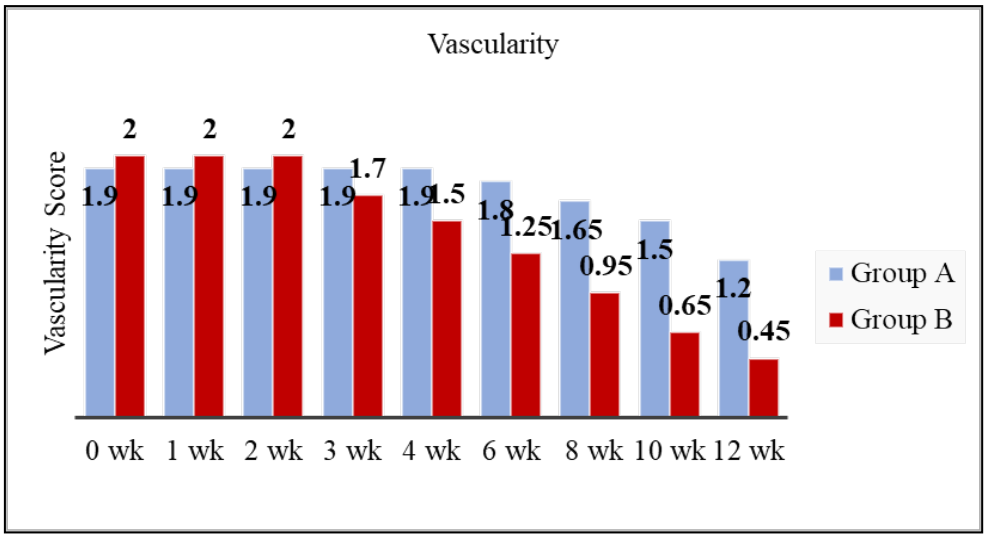

Figure 2: Vascularity score at different weeks in both the groups

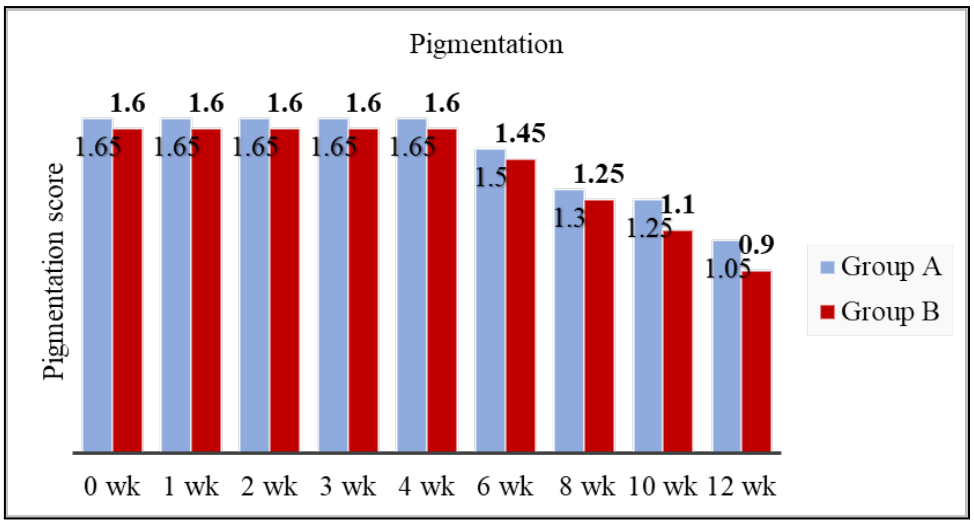

Figure 3: Pigmentation score at different weeks in both the groups

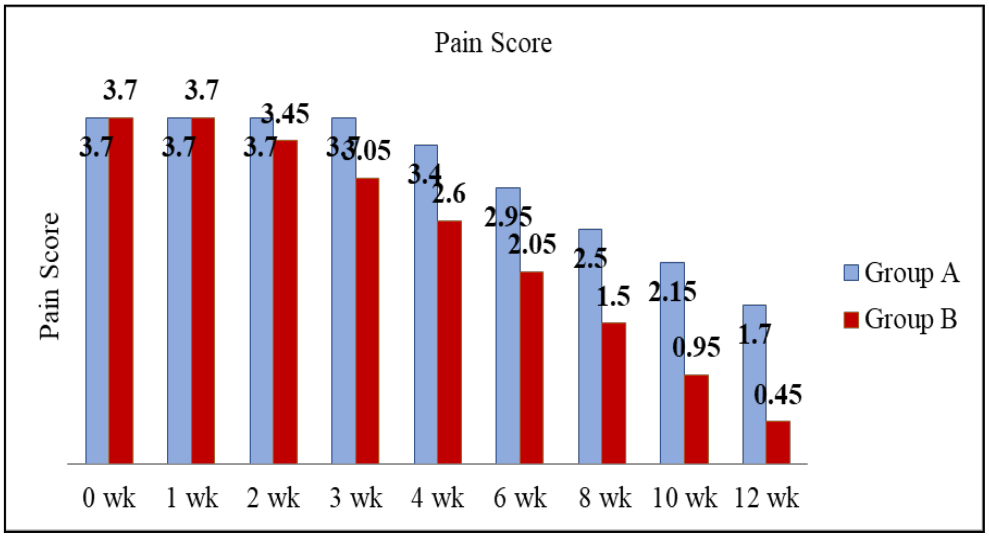

Figure 4: Pain score at different weeks in both the groups

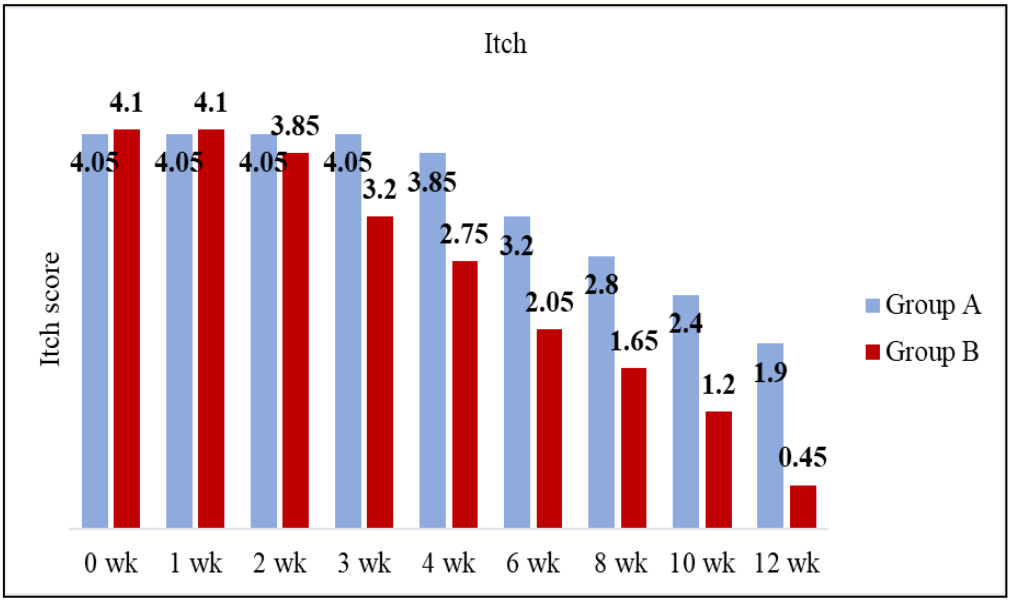

Figure 5: Itch score at different weeks in both the groups

At the end of the study, Group B patients and Group A patients showed improvement in terms of lesion shrinkage (78.69%, 48.72%), vascularity (77.5%,36.84%), pigmentation (43.75,30.3%), itch relief (87.8%,53.09%) & pain relief (87.84,54.05%) respectively. (See table 5 and figure 6)

Table 5: Percentage improvement in Vancouver scar scale and subjective scale scores

Keloid character	Group	2 wk	3 wk	4 wk	6 wk	8 wk	10 wk	12 wk
Volume	A	0		0.68	17.21	28.45	40.89	48.72
	B	0	6.36	21.99	36.25	50.17	63.91	78.69
Vascularity	A	0	0	0	5.6	13.16	21.05	36.84
	B	0	15	25	37.5	52.5	67.5	77.5
Pigmentation	A	0	0	0	9.09	21.21	24.24	30.3
	B	0	0	0	9.37	21.88	31.25	43.75
Pain	A	0	0	8.11	20.27	32.43	41.89	54.05
	B	6.76	17.57	29.73	44.59	54.46	74.32	87.84
Itch	A	0	0	4.94	20.99	30.86	40.74	53.09
	B	4.88	20.73	31.71	48.78	58.54	69.51	87.8

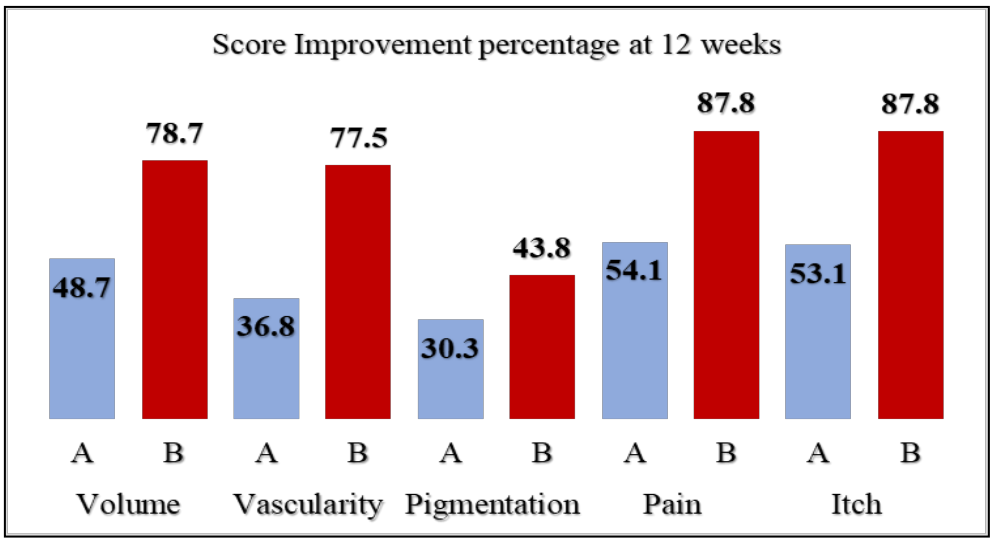

Figure 6: Percentage improvement in Vancouver scar scale and subjective scale scores at week 12 in both the groups

Response to treatment with regard to all parameters was much better in Group B than in Group A. Good to excellent response was seen in >50% patients in both the groups except for keloid volume which was fair to good in Group A. (See table 6)

Table 6: Response in various parameters in both the groups

Parameter	Group	Excellent (76-100%)	Good (51-75%)	Fair (26-50%)	Poor (≤25%)
Keloid volume	A	0	25	75	0
	B	60	40	0	0
Vascularity	A	35	20	15	30
	B	65	25	10	0
Pigmentation	A	22	39	0	39
	B	21	53	0	26
Pain	A	0	62	38	0
	B	85	15	0	0
Itch	A	0	56	44	0
	B	81	19	0	0

All patients in both the groups experienced pain at the injection site. Burning sensation was experienced by 3 patients in Group A and 1 patient in Group B. 3.33% patients had hypopigmentation and hyperpigmentation in Group A and Group B respectively. (See table 7)

Table 7: Safety profile in both the groups

	Group A		Group B	
Adverse effect	**No of Patients**	**Patient %**	**No of Patients**	**Patient %**
Pain at injection site	30	100	30	100
Burning sensation at the injection site	3	10	1	3.33
Hypopigmentation	1	3.33	0	0
Hyperpigmentation	0	0	1	3.33

*Ulceration, telangiectasia, skin atrophy, skin necrosis were not seen in any patient in both the groups

Discussion

Keloids are cutaneous lesions produced as a result of uncontrolled dermal collagen deposition. Intralesional corticosteroid is the first line of treatment in keloids. [14] The first to use intralesional 5FU in combination was Fitzpatrick and he showed it to have good efficacy.[15] A study showed that 5FU alone produced 62.5% efficacy while combination of 5FU with steroid showed an efficacy of 92%.[16]

Mean age in a study was 45±8.2 and 43±3.6 in TAC group and 5FU group respectively which is comparable to that in our study (44±4.6years and 41±3.8 years). [3] A study showed that keloids occurrence was equal in both sexes, which is similar to that in our study. [17]

Studies have shown significant improvements in all parameters using either 5FU alone or 5FU with TAC combination. [3,18,19] A study has shown significant improvement in all parameters except pruritus, [20] while another study done after our study period has shown significant improvement in all parameters except pain.[21] All these studies are similar to that in our study where there was significant improvement in all parameters except pigmentation. A study showed 84% improvement in keloid volume in TAC with 5FU combination while in our study it was 78.69%. [22] Pliability and itch score were the first to improve in a study. [23] whereas in another study, the order of improvement was pain and itch, followed by softening, then flattening and redness which is similar to that in our study except softening which was not assessed in our study. [15] Pain and itch improvement was 82% in a study which is almost concordant to that in our study(87.8%). [24]

Two studies have reported 55% and 80% of patients showing excellent to good response (>50% improvement) in scar flattening in drug combination group, [14,20] while another two studies have reported 95% of patients showing excellent to good response, which is almost comparable to that in our study (100%). [3,19]A study reported pruritus improvement of 96% in drug combination group and 72% in TAC group, [19] while our study showed 87.8% and 53.09% in both groups respectively, which is concordant with another study where it was 85% in drug combination group. [3]

Studies have reported that all patients experienced transient pain at the injection sites which is similar to that in our study, but pain was mild in combined group in our study. [14,15,19,23,25]

!00% patients showed hyperpigmentation when treated with 5 FU alone. [23,25] In contrary, a study using 5FU with TAC combination reported only 4% showing hyperpigmentation, which is comparable to that in our study (3.33%).[19] In that same study burning sensation was 100% which varied from our study (3.33% in combination group and 10% in TAC group).[19] Almost comparable to our study was another study where burning sensation was 7.1% in 5FU group. [14]

No ulcers were noted in our study whereas two studies showed 21.4% and 4% ulcers using 5FU alone. [14,25] Hypopigmentation was nil in combination group and 3.33% in TAC group in our study, similar to that in a study where it was 4% in TAC group and 8% in combination group.[19] Studies have not reported any serious and haematological side effects, which is concordant to that in our study. [14,19,20,23] Considering our study and the compared studies it may be inferred that combination of TAC with 5FU has early improvement in VSS scores, pain and itch. It has better response and significant efficacy compared to TAC alone. So, it can be preferred in the treatment of keloids.

Limitations: As the study was double blinded, observer bias may not be present. Study was done on a very small sample size and for a very short period, so cannot be applied to general population. Pliability of keloids was not assessed, so can be done in further studies which can be conducted on a very large population and at multiple sites simultaneously. Longer duration studies with more injection sessions and longer duration follow up can be done in future studies to see for delayed complications, complete remission and or recurrence if any. Further studies can be done in patients having keloids and other comorbid conditions.

Conclusion

Intralesional injection of combination of 5 Fluorouracil with Triamcinolone has early onset of action, is more efficacious, has better response and is safer than Triamcinolone alone in the treatment of

keloids. So, combination regimen can be considered as a better option to treat keloids rather than Triamcinolone alone.

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