

## Original Research Article

# Comparative study on outcome of intralesional steroid and combination of intralesional steroid with 5-fluorouracil in keloid treatment

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## ABSTRACT

**Background:** Though the definitive management of keloids are not yet established, many treatment modalities have been described which are being used alone or in combination all over the world with some promise. This study aims to assess the effect of intralesional steroids and 5-fluorouracil (5-FU) in the treatment of keloids.

**Methods:** The study included 40 patients with keloids, out of which 20 received 6 doses of intralesional steroid and the other 20 received alternating three doses of intralesional steroid and three doses of 5-FU. The size of the keloid and the POSAS (Patient observer scar assessment scale) score were marked on the proforma and the patient was reassessed after 6 months. The decrease in volume and POSAS score was statistically analysed using paired and unpaired t tests.

**Results:** There is a statistically significant decrease in POSAS score after intervention in both the steroid and steroid+5 FU groups. However, the decrease in POSAS score is significantly more in the group that received steroids alone. The group that received steroids had a greater decrease in volume (50% reduction) compared to the group that received the steroid-5FU combination (27% reduction).

**Conclusions:** There is a statistically significant decrease in POSAS score after intervention in both the steroid and steroid+5 FU groups. However, the decrease in POSAS score is significantly more in the group that received steroids than the group that received steroid-5 FU combination.

**Keywords:** Keloid, Intralesional, Steroid, 5-FU

## INTRODUCTION

Keloids are dense, fibrous tumors that result from the dysregulation of normal wound healing and classically 'outgrow' the original traumatic lesion. The abnormal wound-healing process results from the lack of control mechanisms regulating cell proliferation and tissue repair.

Keloids have always been a cosmetic problem and cause severe psychological problems for the patient. Besides the psychological aspect, the physical and functional implications of keloids and hypertrophic scars are also

significant.<sup>1</sup> The management of hypertrophic scars and keloids remains an unsolved problem. Many therapeutic modalities have been described namely intralesional therapy, pressure therapy, cryotherapy, radiotherapy, surgical excision, and even combinations of these therapies.<sup>2-6</sup> This study focuses on the possibilities that intralesional injections can bring into the therapy of keloids.

The anti-inflammatory and scar-enhancing properties of corticosteroids on hypertrophic scars and keloids have been extensively investigated. They are considered a first-line strategy in the treatment of keloids. The most

commonly used corticosteroid in this matter is triamcinolone acetate, and its efficacy and usefulness as well as its limitations are well known.<sup>7,8</sup>

The antineoplastic drug 5FU effectively induces keloid flattening and is thus widely used for these pathological scars. Although the mechanism by which 5-FU improves pathological scars remains poorly understood, there is some evidence that it may inhibit fibroblast growth and transforming growth factor beta (TGF- $\beta$ ) induced collagen type I expression.<sup>9</sup>

This study aims to compare the change in size and POSAS score of keloids between those patients receiving intralesional steroid and those receiving 5-FU and steroid combination.

## **METHODS**

### ***Study design***

Prospective observational study design was used.

### ***Study setting***

Study conducted at department of plastic and reconstructive surgery, government medical college, Trivandrum.

### ***Study period***

Study carried out for 1 year (January 2022 to January 2023).

### ***Study population***

All patients receiving intralesional treatment for keloid in the department of plastic and reconstructive surgery of government medical college, Thiruvananthapuram

### ***Inclusion criteria***

All men and women above 18 years of age presenting to the department of plastic and reconstructive surgery, government medical college, Trivandrum with complaints of keloid were included in the study.

### ***Exclusion criteria***

Patients who were not willing to give consent, those who had received any other treatment for the keloid in the past 6 months, those who were immunocompromised or those having renal disease, liver disease, or malignancy or those with any allergic reaction to triamcinolone or 5-FU were excluded from the study.

### ***Sample size***

The 40 keloids were included in the study.

## ***Outcome measurement***

Change in size of the keloid and change in POSAS score.

## ***Study procedure***

The patient was made to lie down supine or prone as per the site of the keloid. The local area is sterilized with a spirit swab. For those receiving intralesional steroids, triamcinolone (40 mg/ml) is loaded in an insulin syringe or a 2 ml syringe and injected intra-lesionally with 26G 1-inch needle till the keloid blanches (Figure 1). The same may be repeated at monthly intervals for about 6 doses. For those receiving 5 FU 50 mg/ml of the drug is loaded in the same way and given in the same method. This is alternated with triamcinolone injections at monthly intervals for a maximum of 6 doses.



**Figure 1: Intralesional injection of triamcinolone into a presternal keloid.**

## ***Post procedure advice and follow-up***

Patients were advised not to vigorously rub the face for 12 hours. No dressing was required. The scar was reassessed monthly by measuring the dimensions and photographs for a period of 6 months. At every visit, clinical photographs were taken.

## ***Method of data collection***

All patients who met the inclusion criteria for the study population were taken up for the study after getting their informed written consent. All patients were evaluated with complete blood counts, renal function tests, and liver function tests as per the standard protocol followed in the department. The investigator then fills up the proforma after getting adequate history and proper clinical examination. The keloid size is measured with the help of vernier calipers.

The scar is scored as per the JSS (Japanese scar scale). The Japan scar workshop (JSW) developed the JSS score to differentiate keloids and hypertrophic scars. It consists of two tables. The scar classification table is used to determine whether the scar is a normal mature scar, a hypertrophic scar, or a keloid. The evaluation table is used to judge the response to treatment and follow-up. The classification table consists of two parts: risk factors and present symptoms. Only those with a classification score of more than 15 indicating a keloid scar are taken further into the study. The keloid is further examined and the POSAS score is calculated which consists of two scales: The patient scale and the observer scale. The patient scale was scored by patient himself/herself and observer scale was scored by the principal investigator.

Both treatment methods (intralesional steroid and intralesional steroid + 5 FU combination) are adopted by the staff in the department. So, the investigator just keeps a record of the treatment being given, which is solely decided by the treating surgeon. The treatment modality they are undergoing is also entered into the proforma. The patient was also asked to record the pain they experienced on injection of the drug on a scale from 0 to 10 where 0 indicates no pain and 10 indicates the most severe pain imaginable.

After 3 and 6 months of starting treatment, change in size of keloid is assessed. Also, POSAS scoring was again done to assess change in score on treatment.

### Statistical analysis

The data were collected in a prewritten proforma and were entered into a Microsoft excel spreadsheet. Statistical analyses were performed by using a statistical software package SPSS, version 25. Categorical and quantitative variables were expressed as frequency (percentage) and mean  $\pm$  SD respectively. A comparison of the dependent variable, before and after intervention was carried out using a paired t-test. The change in the outcome between the steroid and 5 FU-steroid combination group was compared using an unpaired t test. A p value less than 0.05 was considered significant.

## RESULTS

In the current study, 55% (n=22) of the population was in the age group 20-30 years, 25% (n=10) was older than 30 years and the rest 20% (n=8) less than 20 years. The study consists of 35% (n=14) males and 65% (n=26) females, 50% (n=20) of patients presented with keloid in the pinna, 15% (n=6) with keloid in the head and neck other than the pinna, and the rest 35% (n=14) with keloid in the trunk and limbs. 80% (n=32) of keloids resulted from piercing injuries, 10% (n=4) from surgical incisions, and rest 10% (n=4) from non-specific injuries.

The present study obtained two groups that were comparable at baseline for most of the variables like age,

location, duration of keloid, cause of injury, family history, and co-morbidities (p>0.05) except gender (p<0.05). All baseline values except the POSAS patient score were comparable at baseline (p>0.05) (Table 1).

**Table 1: Comparison of group variables.**

Variables	Steroid	Steroid + 5 FU
Age (in years)	<20	2
	20-30	14
	>30	4
Gender	Male	10
	Female	16
Site	Pinna	10
	Head and neck	4
	Trunk	6
Duration (in years)	<1	0
	1-2	4
	2-3	8
	>3	8
Cause of trauma	Non specific	4
	Piercing	14
	Surgery	2
Family history	Yes	8
	No	12
Comorbidities	Yes	4
	No	16

**Table 2: Comparison of continuous variables at baseline.**

Variables	Steroid (Mean $\pm$ SD)	Steroid+5FU (Mean $\pm$ SD)	P value
Age (in years)	24.90 $\pm$ 10.25	30.20 $\pm$ 13.99	0.18
JSS score	18.30 $\pm$ 2.00	17.90 $\pm$ 1.48	0.47
JSS before treatment	13.00 $\pm$ 1.21	12.10 $\pm$ 2.17	0.11
POSAS patient scale	38.4 $\pm$ 4.54	35.40 $\pm$ 2.64	0.015
POSAS observer scale	41.20 $\pm$ 5.20	38.90 $\pm$ 4.59	0.14

JSS-Japanese scar scale, POSAS-Patient and observer scar assessment scale, SD-Standard deviation and 5 FU-5 Fluorouracil.

There is a statistically significant decrease in POSAS score after intervention in both the steroid and steroid+5 FU group (p<0.01) (Table 2) (Figure 2-5).

The decrease in POSAS score (both patient and observer scale) is significantly more in the group that received steroids than the group that received steroid-5 FU combination (Table 3).

There is a 49.72% reduction in the volume of keloid in the group that received steroid alone compared to a 26.89% reduction in the volume of keloid in group that

received steroid - 5FU combination. Decrease in volume of keloid in steroid group is significantly higher than that in steroid+ 5 FU combination group (p<0.01) (Table 4).

**Table 3: Comparison of change in mean POSAS score after treatment.**

Treatment	POSAS score	Before treatment	After treatment	Mean difference ± SD	Std error (SE)	95% CI		P value
						Lower	Upper	
Steroid	Patient scale	38.40	30.30	8.1±4.4	0.99	6.02	10.17	<0.001
	Observer scale	41.20	33.50	7.7±4.2	0.95	5.70	9.69	<0.001
Steroid +5 FU	Patient scale	35.40	29.80	5.6±4.38	0.98	3.54	7.65	<0.001
	Observer scale	38.90	34.50	4.4±4.2	0.94	2.41	6.38	<0.001

POSAS- Patient and Observer Scar Assessment Scale, SD- Standard Deviation, 5FU- 5 Fluorouracil.

**Table 4: Comparison of change in scores before and after treatment between steroid and 5FU.**

Diff in scale	5 FU+ steroid (Mean ± SD)	Steroid (Mean ± SD)	Mean difference ± SE	95% CI of mean difference		P value
				Lower	Upper	
Difference in patient scale	5.60±4.3	8.50±3.5	-2.9±1.26	-5.45	-0.344	0.027
Difference in observer scale	4.4±4.23	7.70±4.25	-3.3±1.34	-6.01	-0.582	0.019

5FU-5 Fluorouracil, SD-Standard deviation, SE-Standard error.

**Table 5: Comparison of decrease in volume of keloid on treatment.**

Treatment	Volume before treatment (Mean)	Volume after treatment (Mean)	Decrease in volume (Mean ± SD)	Reduction in volume (%)
Steroid	7.20	3.62	3.58±2.94	49.72
Steroid + 5 FU	4.24	3.10	1.14±1.6	26.89

5FU-5 fluorouracil, SD-Standard deviation.

Also, it was found that the pain reported by the patient on injection of 5-FU (mean: 7.65±1.04) is significantly higher than the pain on injection of steroid (mean: 5.90±0.91) (p<0.01).

Figure 2 shows patient A who presented with post surgical post auricular keloid who was treated with 6 doses of intralesional steroid. Figure 3 of the same patient shows the decrease in size of keloid after treatment.

Figure 4 shows patient D with keloid in pinna which developed after ear piercing. She was treated with alternating doses of steroid (3 doses) and 5-FU (3 doses). Figure 5 shows mild flattening of keloid after treatment.



**Figure 3: Post auricular keloid in patient A after six doses of steroid.**



**Figure 2: Post auricular keloid in patient A before treatment.**



**Figure 4: Ear lobe keloid in patient D before treatment.**



**Figure 5: Ear lobe keloid in patient D after six doses of combined steroid-5-FU treatment.**

## DISCUSSION

Keloids can be defined as benign tumors of the skin arising as a result of abnormal response to wound healing. It is pathologically characterised by the excessive proliferation of dermal fibroblasts and the resultant exuberant deposition of abnormal collagen. Clinical features include unsightly swellings, itching, pain, anxiety and depression. Though there is much research going on about keloids, the exact cause for keloid formation has not been fully understood. Hence there is no gold standard treatment modality for the same. Multiple therapeutic modalities, with variable success, have been reported, with intralesional steroids and intralesional 5-FU being two among them with the former being used more commonly worldwide. It is used either alone or as an adjunct to cryosurgery or surgical excision or in combination with 5-FU.<sup>10</sup>

The present study had a sample size of 40 who fulfilled the inclusion criteria. 20 of them received intralesional steroids for 6 doses at 4 weekly intervals and the other 20 received alternate steroid and 5 FU doses (total three steroid and three 5-FU doses) at similar 4 weekly intervals. They were evaluated for improvement in keloid characteristics at the end of 6 months. Changes in POSAS score and the volume of keloid were taken as the outcome measurements.

The 55% (n=22) of the population was in the age group 20-30 years, 25% (n=10) was older than 30 years and the rest 20% (n=8) less than 20 years. The study consists of 35% (n=14) males and 65% (n=26) females. 50% (n=20) of patients presented with keloid in the pinna, 15% (n=6) with keloid in the head and neck other than the pinna, and the rest 35% (n=14) with keloid in the trunk and limbs. 80% (n=32) of keloids resulted from piercing injuries, 10% (n=4) from surgical incisions, and rest 10% (n=4) from non-specific injuries. Though this was not a randomized clinical trial, the study obtained two groups that were comparable at baseline for most of the variables except gender and the POSAS patient scale.

Though intralesional steroid is the more common treatment worldwide, studies on the effect of intralesional 5-FU on the treatment of keloids are also available. Nanda et al and Kontochristopoulos et al published a study of patients treated with 5-FU alone.<sup>11,12</sup> Though both of them reported a 70 to 95% success rate for the drug, neither of these studies were a randomized controlled trial. Sadeghinia et al conducted a randomized controlled trial with 44 patients comparing the efficacy of 5 FU and triamcinolone injections.<sup>13</sup> Both patient-reported and observer reported outcomes indicated that 5-FU injections produced significantly better results compared to triamcinolone injections.

Prabhu et al did a study comparing the efficacy of weekly intralesional injections of 50 mg/ml 5-FU versus 40 mg/ml triamcinolone (control) in 30 patients with keloids for 4 weeks.<sup>10</sup> Interestingly, good to excellent flattening of keloid size was seen in 64% of patients in patients receiving 5-FU versus 87% in patients receiving triamcinolone alone, and the difference was proved to be statistically significant. Though various complications like ulceration, pruritis and pain was reported during 5-FU injections, it was not statistically significant.

In the study by Heitanen et al they compared the efficacy of intralesional 5-FU and triamcinolone injections in a double-blind randomized controlled trial.<sup>14</sup> Forty-three patients with 50 keloid scars were treated with either intralesional triamcinolone or 5-FU injections over 6 months. However, there was no statistically significant difference in the remission rate at 6 months between both the groups (46% in 5 FU group and 60% in triamcinolone group). The study observed a positive response in both the groups and proved the improvement between the baseline and 6 months to be statistically significant. However, the remission rate after 5-FU treatment was lower than in previous studies mentioned above.

In the study by Davison et al 102 keloids were observed.<sup>9</sup> 52 keloids were treated with an intralesional injection of combination 5-FU/steroid without excision. The 24 keloids were treated with a combination of 5-FU/steroid with excision, 26 keloids were treated with steroid alone followed by excision. Patients who underwent the 5 FU/steroid combination with excision had a 92% average reduction in keloid size compared with 73% in those patients who did not receive 5 FU. Patients who received intralesional 5-FU/steroid without excision had an average size reduction of 81%. In the present study, there is a 49.72% reduction in the volume of keloid in the group that received steroid alone compared to a 26.89% reduction in the volume of keloid in the group that received steroid-5FU combination. This decrease in the volume of keloid in the steroid group is significantly higher than that in the steroid+ 5 FU combination group.

In the study by Srivastava et al, pain at the injection site was a common problem in the 5FU group (140/166 injection episodes, 84%) compared to the steroid (42/170,

24%) and steroid+ 5 FU (58/168, 34%) groups.<sup>15</sup> Also, 9 out of 20 patients who received 5 FU had ulceration and 5 out of 20 patients who received combination steroid- 5 FU had skin ulceration. In the present study, the pain reported by the patient on injection of 5-FU is significantly higher than the pain on injection of steroid. The mean pain score on injection of 5 FU was 7.65 compared to 5.90 in the steroid group. Also, no reports of skin ulceration or erythema were noted.

In the present study, there is a statistically significant decrease in POSAS score after intervention in both the steroid and steroid+5 FU groups. However, the decrease in POSAS score (both patient and observer scale) is significantly more in the group that received steroids than the group that received steroid-5 FU combination.

Also, there is a 49.72% reduction in the volume of keloid in the group that received steroid alone compared to a 26.89% reduction in the volume of keloid in the group that received a steroid-5FU combination. The decrease in the volume of keloid in the steroid group is significantly higher than that in the steroid+ 5 FU combination group. The pain reported by the patient on injection of 5-FU is significantly higher than the pain on injection of steroid.

By regression analysis models it was evidenced that male patients are likely to have a better response than females. Also, keloids in the trunk and limbs are likely to have better responses than those in the ear lobe and head and neck region. Patients with a positive family history also have better results with intralesional therapy. However, it is evident that only up to 40% of the factors affecting the result of intralesional therapy could be studied and that further research is required to identify the remaining factors that are likely to affect the outcome of intralesional therapy, either steroid or 5 FU.

### **Limitations**

Though POSAS scoring system is internationally accepted, it has inter- observer variability. Also, the calculation of volume of the keloid using vernier calipers is not very accurate especially in cases of lobulated or nodular keloids. Use of newer 3D imaging techniques would have increased the accuracy of the volume measurements.

Though the follow up period of the study (6 months) was adequate for the present study, is inadequate for assessing long term results. Since keloid is well known for its long term recurrence, a longer follow up period is more desirable.

The various other other factors that could have affected the outcome of the therapy like genetic factors, immune response as well as individual fibroblast activity could not be studied and was not taken into account during data collection.

### **CONCLUSION**

There is a statistically significant decrease in POSAS score after intervention in both the steroid and steroid+5 FU groups. However, the improvement in keloid characteristics as evidenced by the decrease in POSAS score was more in the group that received steroid than the group that received steroid-5FU combination.

The group that received steroids had a greater decrease in volume (49.72% reduction) compared to the group that received the steroid-5FU combination (26.89% reduction). The decrease in the volume of keloid in the steroid group is significantly higher than that in the steroid+ 5 FU combination group. Also, the pain on intralesional injection of 5FU was reported to be higher than the pain on injection of steroid.

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