

A Comparative Cohort Study of Efficacy of Intralesional Steroid with 5-fluorouracil in the Treatment of Keloid

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Abstract

Introduction: Keloid is a result of fibrosis caused by extracellular matrix over-expression, and angiotensin II through AT1 receptor is known to play a key role in the stimulation of fibrosis. Treatment of keloid is a challenge due to the paucity of effective and universally accepted treatment modalities and their high recurrent nature. 5 fluorouracil (5-FU) is known to seize fibroblast proliferation in fibroblastic tissue cultures due to its antimetabolite activity without any major side effects. The goal of this study is to normalize the usage of 5-FU in routine keloid treatment.

Materials and Methodology: In this study, we have compared the efficacy of intralesional steroid and intralesional steroid with 5-fluorouracil in the treatment of keloid. It is a prospective cohort study with 50 patients, done over period of 5 months, where one group (Group A) received only intralesional triamcinolone and Group B received intralesional triamcinolone with 5-FU. This study included all the patients with keloid visiting AMCH plastic surgery department, study excluded patients with below 10 years, patient who were already on steroid injection/inhalational/oral, and patient who received treatment for keloid in the past 3 months. The results are noted down by the third observer in the data sheet using clinical tools (scale, measuring compass).

Results: Group A patients (25) showed 28.07% reduction in length, 31.11% reduction in breadth, 9.46% reduction in surface area, and 34.78% reduction in thickness whereas Group B (25) showed excellent results with 34.42% reduction in length, 32.31% reduction in breadth, 12.56% reduction in surface area, and 48.74% reduction in the thickness ($P \leq 0.05$).

Conclusion: 5FU aids in the reduction of keloid and also increases the efficacy of steroids.

Key words: Keloid, 5-FU (5-fluorouracil), Triamcinolone

INTRODUCTION

Keloid is a result of fibrosis caused by extracellular matrix over-expression, and angiotensin II through AT1 receptor is known to play a key role in the stimulation of fibrosis. Treatment of keloid is a challenge due to the paucity of effective and universally accepted treatment modalities and

their high recurrent nature. 5 fluorouracil (5-FU) is known to seize fibroblast proliferation in fibroblastic tissue cultures due to its antimetabolite activity without any major side effects. The goal of this study is to normalize the usage of 5-FU in routine keloid treatment.^[2-6]

BACKGROUND/RATIONALE

Explain the science these lesions have a high incidence in darker skin individuals, but the exact figure is different in different studies and ranges from 4.5% to 16%. Despite being in the limelight, there is still no single treatment with predictable outcome. The traditional treatments usually result in recurrence. Although modern scar treatments claim good

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results, still need to be proven by good-quality clinical trials. In addition, the side effects of conventional treatment, i.e. steroid injections, are common and significant. In this scenario, the ideal treatment should have lesser side effects, low cost, and does not require any hardware for administration. The use of antineoplastic agents as a treatment option is logical because this abnormal tissue is in hypermetabolic state. 5-FU has been known to affect 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 the use of pure 5-FU injection. Intralesional 5-FU is, however, safe and does not have systemic toxicity as compared to its intravenous use.

Objectives

The objectives of the study are to compare the study of efficacy of intralesional steroid with 5-fluorouracil in the treatment of keloid.

METHODS

Study design

This is a prospective cohort study.

Setting

This study will be conducted in the Department of Plastic Surgery, Assam Medical College. It is a cohort study conducted on all patients clinically diagnosed with keloid after obtaining informed consent.

Participants

Inclusion criteria

All the patients who are clinically diagnosed with keloid.

Exclusion criteria

Age below 10 years, patient who is already on steroid injection/inhalational/oral, pregnant, and patient who received treatment for keloid in the past 3 months. The results were measured by third observer using clinical used tools – scale and measuring compass.

Variables

Two variables are considered – Group A and Group B. Group A patient (25) showed 28.07% reduction in length, 31.11% reduction in breadth, 9.46% reduction in surface area, and 34.78% reduction in thickness whereas Group B (25) showed excellent results with 34.42% reduction in length, 32.31% reduction in breadth, 12.56% reduction in surface area, and 48.74% reduction in the thickness ($P \leq 0.05$). There were no other drug exposures nor any other confounding factors in the study.

Data sources/measurement

After obtaining the ethical clearance from the AMCH, ethical committee study was started.

All the patients who are clinically diagnosed with keloid are randomly divided into two groups – Group A and B. Group A patients received injection of triamcinolone 20 mg/mL mixed with 2% xylocaine solution 1:1 ratio and injected up to the depth of 3–5 mm with insulin syringe. The injections were given at the interval of 1 week for 8 weeks and Group B received 5-FU intralesional injections 50 mg/mL in given intralesional after the test dose. As it cannot be mixed with lignocaine solution, the area was pre-filtrated with the 2% xylocaine infiltration, and then, 5-FU was injected. Here, only single dose was administered.

Patients were followed up on weekly basis.

Bias

Third observer noted the results to avoid bias.

Study size

Based on the number of patients visiting the department of AMCH plastic surgery outpatient department (OPD) who are diagnosed with keloid, sample size was calculated using $n = Z^2p(1 - p)/m^2$. n is the sample size, Z is the z-value, p is the proportion of population (generally taken as 0.5), and m is the margin of error.

Quantitative variables

Variable 1 is Group A results and Variable 2 is Group B results in terms of surface area, thickness, and length of the keloid before and after treatment in both Groups A and B.

Statistical methods

- t-test: Paired two samples for means
- No subgrouping
- Follow-up was done on the weekly basis till 8 weeks of treatment.

RESULTS

Participants

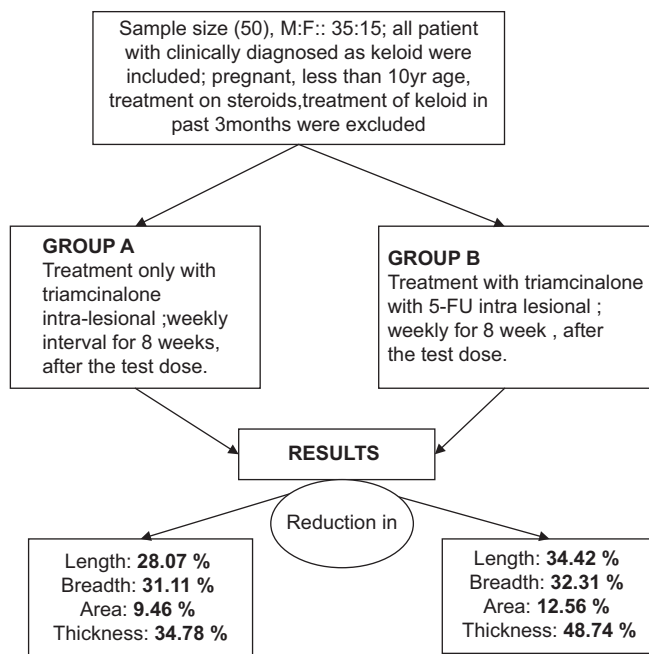
- The study is conducted in a single stage over a period of 5 months, individuals considered for study were explained about the study and need for weekly intervention and follow-ups. After obtaining informed consent and ruling out exception criteria, patients were involved in the study. A total of 50 patients were included in the study. The data were measured by third observer using clinical scales to avoid bias.
- Patient who is willing for pregnancy is discontinued from the study.
- Descriptive data: (i) The population involved in the study were belongs to north-east part of India, mainly Assam state. As the keloid and its outcome also depends on the race of the population; either black /white population were not included in the study.

There were no other environmental/social/economical factors noted that would alter the study outcome. There were no dropouts in the study. All the patients (50) were followed up on the weekly basis in the plastic surgery department OPD, with the allotted treatment received timely. This process continued for 8 weeks. Then, the results were analyzed.

Outcome data

In this study, four main outcomes were considered before and after the intervention was done: (1) Length of the keloid, (2) breadth, (3) area of the keloid, and (4) thickness of the keloid. Furthermore, we considered the cause of keloid and categorized into post-surgical and non-surgical. Furthermore, pigmentation (increase/decrease) over the lesion was noted in this study.

Flow chart:



Main results

a) Data analyzed using $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS software, V.22. (1).1. SPSS I. IBM SPSS Statistics Version 22 Statistical Software: Core System Users’ Guide. SPSS Inc. 2018. Data were also pictorial analyzed with appropriate bar diagram, pie diagram, and stacked bar diagram. Descriptive statistics were used to analyze data in evidence with the study’s objectives. Data were expressed as the mean, 95% confidence interval (CI, lower, and upper bounds), median, minimum and maximum, and percentage, where appropriate. Categorical outcomes were compared between study groups using student t-test with two variables.

Table 1: Paired t-test for mean values of length of keloid

t-test: Paired two samples for means: Length of the keloid:		
Area of reduction of keloid	Variable 1	Variable 2
Mean	2.46	1.87
Variance	1.314693878	0.947041
Observations	50	50
Pearson correlation	0.813710007	
Hypothesized mean difference	0	
df	49	
t Stat	6.248259085	
P (T<=t) one-tail	4.84297E-08	
t critical one-tail	1.676550893	
P (T<=t) two-tail	9.68594E-08	
t critical two-tail	2.009575237	

Table 2: Paired t-test for mean values of breath of keloid

t-Test: Paired two samples for means: Breath of the keloid		
Area of reduction of keloid	Variable 1	Variable 2
Mean	2.32	1.72
Variance	1.201633	0.654694
Observations	50	50
Pearson correlation	0.60928	
Hypothesized mean difference	0	
df	49	
t Stat	4.81773	
P (T<=t) one-tail	7.21E-06	
t critical one-tail	1.676551	
P (T<=t) two-tail	1.44E-05	
t critical two-tail	2.009575	

Table 3: Paired t-test for mean values of thickness of keloid

t-Test: Paired two samples for means: Thickness of the keloid		
Area of reduction of keloid	Variable 1	Variable 2
Mean	0.31	0.204
Variance	0.030714286	0.022433
Observations	50	50
Pearson correlation	0.884780724	
Hypothesized mean difference	0	
df	49	
t Stat	9.158400239	
P (T<=t) one-tail	1.71394E-12	
t critical one-tail	1.676550893	
P (T<=t) two-tail	3.42788E-12	
t critical two-tail	2.009575237	

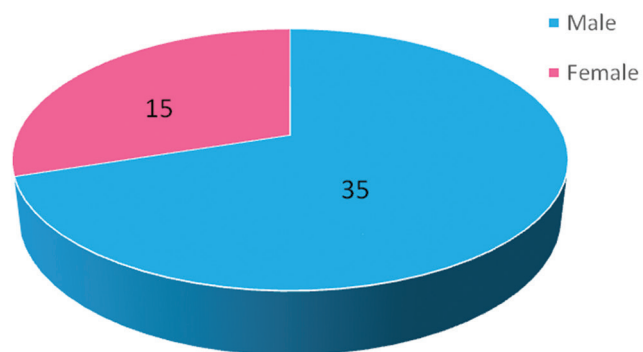
Table 4: Mean measurements of group A before treatment

before treatment		
Average of length	Average of breadth	Average of thickness
2.6	2.08	0.324
0.64	0.56	0.096
2.28	1.8	0.276
28.07	31.11	34.78

INDIVIDUAL ANALYSIS AND RESULTS

Other observation

Amongst the study participants, 68% (34) showed no pigmentation over the injected site; rest 42% (16) showed blackish pigmentation over the lesion. 66% (33) keloid developed over the surgical scar; 24% (12) were over the traumatic scar healed by secondary intention, and 10% (5) were spontaneous in onset [Figures 1-3 and Tables 1-8].



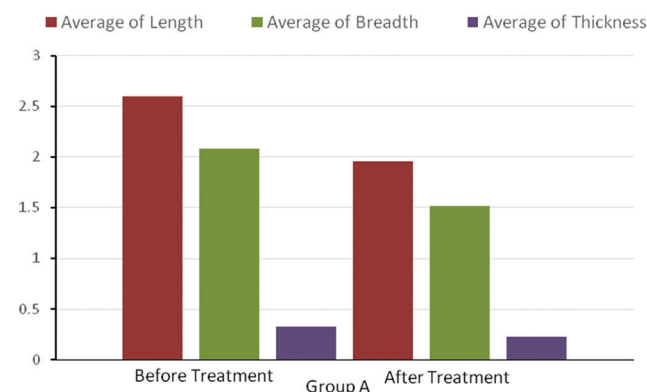
DISCUSSION

Key results

5-FU is an anticancer drug which can also be used locally in the effective treatment of keloid or hypertrophic scar. The side effects of 5-FU are noted majorly depending on the route of administration, dose, and interval between

Table 5: Mean measurements of group after treatment

Group A		Group B	
Area before	Area after	Area before	Area after
6.2	3.9	5.64	3.44
0.56	0.46		
5.92	3.67		
9.46	12.53		



the administration. Here, the dose is 0.1 mL, given intralesionally weekly; hence, 5-FU can be safely used.

The management of keloids is ever-evolving with no universally effective treatment. Corticosteroids have been a popular treatment since mid-1960. Triamcinolone acetonide is the preferred steroid for intralesional injection because of its advantages of longer duration of action, slower release, and lesser chances of pituitary adrenal axis suppression. If we analyze our results with the reported results of several other studies, most of them show comparable results. There are no precise guidelines for the use of radiofrequency in keloids, and the relative inefficacy

Table 6: Mean measurements of group B before treatment

Average of length	Average of breadth	Average of thickness
2.52	2.66	0.296
0.74	0.74	0.116
2.15	2.29	0.238
34.42	32.31	48.74

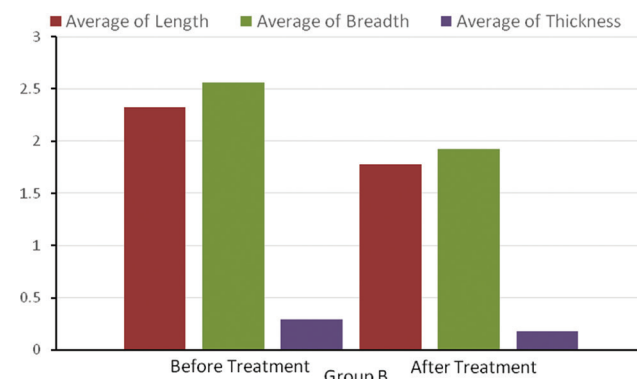


Table 7: Mean measurements of group B after treatment

Average of length	Average of breadth	Average of thickness
1.78	1.92	0.18

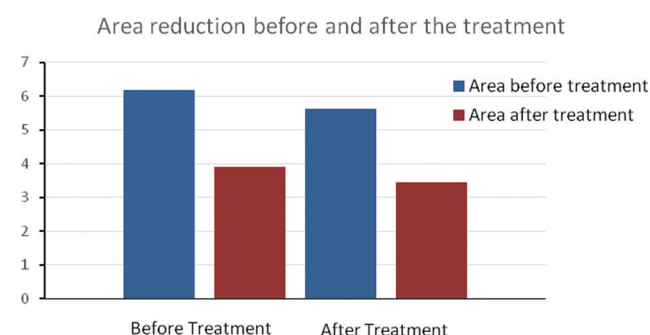


Table 8: Area of reduction of keloid

Group A		Group B	
Area before	Area after	Area before	Area after
6.2	3.9	5.64	3.44
0.56	0.46		
5.92	3.67		
9.46	12.53		

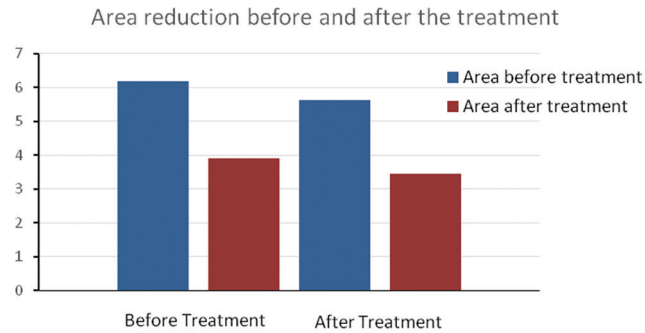


Figure 1: Post-appendicectomy keloid -before and after and after treatment

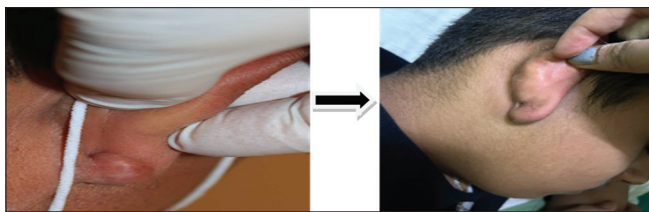


Figure 2: Keloid over ear lobule (before and after treatment)

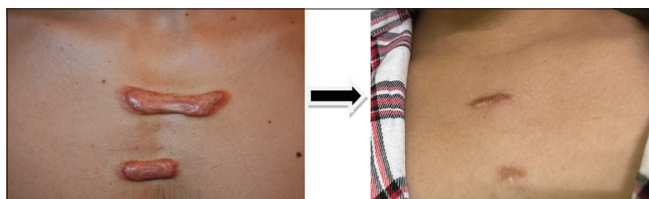


Figure 3: Keloid over the chest (before and after treatment)

of radiofrequency in our study may be because of the different treatment parameters used. We used monopolar ablative radiofrequency with a maximum power output of 90 watts at low to medium settings till blanching of the lesions.

In addition, the previous studies were performed on only auricular keloid, which is known to have better prognosis than keloids in other areas. There are many other modalities

available in the field of plastic and reconstructive surgery today, and few of the others are intralesional verapamil injection and hyaluronidase injections. This collagen remodeling is what is called radiofrequency tissue volume reduction (RFTVR) many others, but all these injectables show variable and non-satisfactory results and RFTVR is invasive procedure which needs multiple settings and costly procedures with not many satisfactory outcomes. Here, in our study, we have considered intralesional 5-FU because of its ease of availability, economical, least adverse effect, ease of the procedure (done on OPD basis), and better satisfactory outcome. Its time we normalize the use of 5-FU and use it as a standard in the treatment of keloids.

Limitations

The intervention cannot used on pregnant or lactating woman and also patient on steroid treatment. The study may need large sample size with involving the multiple centers for more accurate results.

Interpretation

5FU aids in the reduction of keloid and also increases efficacy of steroid. This study establishes that it is effective, safe, economical, and ease of administration with minimum side effects.^[7-13]

CONCLUSION

This study clearly showcased that 5-FU can be used for the keloid treatment, it's a easy, efficient, economical and also showed early results with bare minimum adverse effect.

The phobia toward the side effects of the drugs to be reduced as it is seen when usually when given systemically. Normalise the usage of 5-FU intra-lesionally for the keloid treatment.

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