Original Article

Comparison of 5 Fluorouracil and Triamcinolone acetonide intralesional injection in the management of keloid

Hyder Ali, Madiha Siddique, Mujtuba Pervez, Suneel Kumar, Waqas Sami

Department of Plastic Reconstructive Surgery, Dow University of Health Sciences, Dr Ruth KM Pfau Civil Hospital, Karachi, Pakistan

Objective: To compare the effectiveness of intralesional 5-fluorouracil (5-FU) alone and in combination with triamcinolone acetonide (TAC) for treating keloids.

Methodology: This descriptive comparative study was conducted from June 2018 to February 2019 at Department of Plastic & Reconstructive Surgery, Dow University of Health Sciences and Dr. Ruth KM Pfau Civil Hospital, Karachi. Total 60 patients with keloid at different body part were randomly allocated into two groups. Group A was given 50mg/ml 5-FU intra-lesion while in Group B; in addition to 5-FU 50mg/ml (0.9 ml), 40 mg/ml triamcinolone acetonide (0.1 ml) was given intralesionally. The duration of treatment was 6 months during which injections were given at weekly intervals for four weeks, then twice a month for two months and then once a month until the keloid lesions in both groups assumed virtually the same level as that of surrounding tissue or for a maximum of 3 months.

Results: The mean age of the patients was 35.97±8.28 years. Efficacy was significantly higher in group B as compared to group A (p=0.020).

Conclusion: Patients who received intra-lesion 5-fluorouracil (5-FU) in combination with triamcinolone acetonide (TAC) showed better results in treatment of keloid as compared to 5- FU alone. (Rawal Med J 202;45:549-553).

Keyword: Keloids, Intralesional 5-fluorouracil (5-FU), Intralesional triamcinolone acetonide.

INTRODUCTION

Keloids are disorders of skin with unknown etiology where scar grows outside the original wound boundary. Healing of wounds is a complex physiologic response of the body to trauma and change in the arrangement of this process leads to scars that are exuberant.[1,2] They can be painful, itchy and have an impact on the quality of life.[3] Phenotypes vary due to differences of location, size and amount (raised, pigmented, painful, pruritic) of the lesion.[4,5] Approximately, 5-15% of the wounds can complicate into keloids and both sexes are equally affected although the incidence is higher amongst women.

The average age of onset is 10-30 years. They may develop within a year of the injury and enlarge outside the boundary of the scar margin. High skin tension areas frequently develop keloids i.e. shoulders, chest, neck, flexor surface of extremities and wounds that cross the skin tension lines. Secondary intention wound healing in which the healing time is above 3 weeks is considered as one of the important factors for keloid's development. Etiology of keloids is not clear, but is likely due to environmental and genetic factors.[6,7]

Various therapeutic options like laser therapy, compression therapy, drugs, surgical excision, 5-fluorouracil, silastic gel sheet, radiotherapy, intra-lesion corticosteroids and cryosurgery have been proposed for treating keloids without satisfying outcomes.[8] 5-FU is a pyrimidine analog that inhibits the synthesis of deoxyribonucleic acids by irreversibly inhibiting thymidine synthase, responsible for converting uridine to thymidine.[9] Scarcity of thymidine monophosphates results in thymidine less death in rapidly dividing cells.[10] Triamcinolone acetonide, which is a steroid preferred for intra-lesion treatment of mature keloids as it causes atrophy. It is also given post-operatively to prevent recurrence of keloids that have been excised.[11] It is a potent steroid that localizes within the area of injection and has powerful anti-inflammatory effect.[12] 5-FU has an anti-metabolite property that effects the fibroblast proliferation of the tissues. Triamcinolone acetonide given along with 5-FU may decrease the

locally occurring complications that may occur with use of 5-FU alone.[13]

Different studies around the world have shown different results using only 5-FU and together with triamcinolone acetonide for keloids. Therefore, this study was conducted to improve the evidence level and to evaluate the efficacy of intra-lesion 5-FU alone and with combination of triamcinolone acetonide in terms of more than or equal to 50% reduction in initial scar height.

METHODOLOGY

This descriptive comparative study was carried from June 2018 till February 2019. Approval from Institutional Review Board of Dow University of Health Sciences, Karachi, Pakistan was obtained and a written informed consent was taken. Study included 60 patients with ages 20-60 years of either gender for more than 6 months with dimensions of 1 to 5 cm in size. Sample size was calculated using Raosoft taking 72% in 5- FU response group (%)[6] and 96% in 5-FU with TCA response group (%)[6], 90% confidence interval and 80% of power. Randomization was done by using the lottery method and participants were divided into two groups of 30. Patients who have had scar management treatment in preceding 6 months, or who had abnormal liver function test, serum creatinine >1.2 mg/dl, chronic renal failure or WBC count of <4,000 or >11,000 cells, pregnant women or planning pregnancy and lactating mothers were excluded.

Demographic details like age, sex, weight, height and BMI were recorded. History of each patient was taken inquiring specially the duration of illness and initial injury leading to keloid formation. Investigations like hemoglobin, total leukocyte count; differential leukocyte count was done in each case. In Group A, intralesional injection of 50mg/ml 5-FU was given using 27-gauge insulin syringe. In Group B, in addition to 5-FU 50mg/ml (0.9 ml), 40 mg/ml triamcinolone acetonide (0.1 ml) i.e. concentration ratio of 9:1 was given using same route and method. Injections were 1 cm apart taken 0.1 ml of each of the solutions.

Thereafter, they were advised to report for checkup after 48 hours. Duration of treatment given was 6 months where every week for 4 weeks, the procedures were repeated, then twice a month for two months and then once a month for a maximum of 3 months. Every time, lesions were examined for flatness and recurrence. Pre and post treatment photographs were taken. All participants were advised massage and compression therapy after the procedures and it was continued for 6 months. Participants who developed skin necrosis as a complication were managed with daily dressings and were left for healing with secondary intention.

Effectiveness of the therapy was measured in terms of more than or equal to 50% reduction in initial scar height. The scars were assessed on a Scar Assessment Scale[1] where no improvement (no height reduction of the scar) was given score of 0, poor (0-25% height reduction) was given as score of 1, fair (25-50% height reduction) was given score 2, good (50-75% height reduction) was given 3 and excellent (75-100% height reduction) was given a score of 4.

Statistical Analysis: Data were analyzed using SPSS version 20. Reduction in height of the keloid as per the scar assessment scale was done and compared in terms of efficacy by applying chi square test. $p< 0.05$ was considered statistically significant.

RESULTS

Out of 60 participants, 28 (46.7%) were male and 32 (53.3%) female. The average age of the participants in Group A was 34.97±8.05 years and in Group B was 36.97±8.53 years. The mean weight (kg) of the participants in Group A was 75.50±17.60 and in Group B was 74.58±16.83. Mean height (cm) in Group A was 164.55±10.08 and in Group B, it was 162.85±8.23. In terms of BMI (kg/m^2), it was 27.78±5.54 in Group A while in Group B, it was 28.12±6.32. Anatomical location of keloid lesion in both groups shown in Table 1.

Table 1. Sites of keloids.

Sites	Group A	Group B
Pre sternal area	11 (36.6%)	9 (30%)
Shoulder	7 (23.3%)	9 (30%)
Ear	6 (20%)	7 (23.3%)
Upper Limb	4 (13.3%)	3 (10%)
Lower Limb	2 (6.6%)	2 (6.6%)

Table 2. Comparison of Mean Reduction of Keloid.

Keloid lesions	Group A n=30		Group B n=30		p-Value
	Mean	Std. Deviation	Mean	Std. Deviation	
Height of keloid before treatment (cm)	3.30	1.34	3.33	1.37	0.925
Height of keloid after treatment (cm)	2.10	1.51	1.12	1.23	0.0008
Percent Reduction (%)	43.40	26.42	72.83	30.80	0.0005

Table 3. Effectiveness of treatment.

Efficacy	Group A n=30	Group B n=30	Total	p-Value
Yes	18 (60%)	26 (86.7%)	44 (73.3%)	0.020
No	12 (40%)	4 (13.3%)	16 (26.7%)	

Chi-Square = 5.455 p=0.020

Table 4. Effectiveness for treatment with respect to age.

Age Groups	Efficacy	Group A n=30	Group B n=30	Chi-Square	p-Value
≤40 Years	Yes	13 (59.1%)	17 (94.4%)	6.599	0.013
	No	9 (40.9%)	1 (5.6%)		
	Total	22	18		
>40 Years	Yes	5 (62.5%)	9 (75%)	0.357	0.642
	No	3 (37.5%)	3 (25%)		
	Total	8	12		

No significant difference of mean height of keloid (cm) before treatment was observed in both groups while reduction of mean height of keloid after treatment and percent reduction in height was significantly less in group B as compared to group A (p=0.0008) (Table 2). Efficacy was found to be significantly higher in group B as compared to group A (86.7% vs. 60% p=0.020) (Table 3).

Stratification analysis for age was performed and it was observed that the efficacy in group B was significantly higher than group A for age 40 years or below while it was not significant for above 40 years of age (p=0.013) (Table 4). Efficacy was although higher in group B than group A but it was not significant after the stratification of male and female (p=0.066 for males, p= 0.337 for females). Stratification of weight (p=0.013) and height (p=0.074) were also observed to be significantly different between groups in those cases who had more than 75 kg and height of more than 160 cm.

DISCUSSION

A keloid hyper-proliferative growth, composed mainly of either type III collagen in the early phase or type I collagen in the late phase.[14,15] In our study, efficacy of combination of 5-FU and triamcinolone acetonide (TAC) was significantly higher in group B as compared to group A which was treated with 5-FU alone [86.7% vs. 60% p=0.020]. A recent meta-analysis concluded that TAC +5FU is safer and more efficacious than TAC alone.[16] Sharma et al concluded that 5-FU in combination with TAC of small keloids was a better modality compared with 5-FU alone. In 96% cases in group of combination of 40 mg/ml triamcinolone acetonide and 5-Fu, good to excellent response was seen.[17] Davison et al demonstrated that the combination 5-FU/triamcinolone resulted in 92% average reduction in size of lesions.[18]

A study comparing both 5-FU and in combination with TAC observed improvement in all parameters.[19] A very recent study compared TAC alone and in combination with 5-FU concluded that both were effective in treatment of keloids although triamcinolone alone had higher relapse rate and combination therapy was more effective with faster results and few side effects.[20] Srivastava et al showed statistically significant improvement in terms of height, vascularity and pliability was fastest with 5FU and triamcinolone acetonide.[21]

Triamcinolone acetonide has been used dose of 10–40mg/ml. We chose dose of 40mg/mL for our study, as higher doses lead to more complications. Telangiectasia, skin atrophy, and altered pigmentation are the most frequent adverse effects linked to TAC.[22,23] As a combination; TAC has been added to 5-FU in a ratio of 1:9, which translates to a TAC concentration of 4 mg/ml. This dose may not be sufficient by itself in scar regression, but it plays a different kind of role by limiting the adverse effects of 5FU by its anti-inflammatory nature. The outcomes of this study in the TAC+5-FU group are comparable to those reported earlier.[24]

A limitation of this study was the shorter duration of follow-up. All patients in our study were observed

for 6 months, during which there was no recurrence. In such a prospective study, long-term follow-up is difficult. Our interaction with such patients leads us to believe that this is probably because the patient is unwilling to return when they are convinced that the disease has been apparently cured. Perhaps a longer prospective study focusing on recurrence might prove more useful in this regard.

CONCLUSION

Our results show that patients who received intra-lesion 5-fluorouracil (5-FU) in combination with triamcinolone acetonide showed better results in treatment of keloid as compared to (5- FU) alone. Therefore, it is recommended to use this combination therapy as an effective method of treatment for keloids.

Authors contribution:
Conception and design: Hyder Ali
Collection and assembly of data: Madiha Siddique, Suneel Kumar
Analysis and interpretation of the data: Madiha Siddique
Drafting of the article: Mujtuba Pervez
Critical revision of the article for important intellectual content: Hyder Ali
Statistical expertise: Waqas Sami
Final approval and guarantor of the article: Hyder Ali
Corresponding author email: Hyder Ali: hyder.ali@duhs.edu.pk
Conflict of Interest: None declared
Rec. Date: Dec 6, 2019 Revision Rec. Date: May 12, 22020 Accept Date: Jun 16, 2020

REFERENCES

1. Muhammad AK, Bashir MM, Khan FA. Intralesional triamcinolone alone and in combination with 5-fluorouracil for the treatment of Keloid and Hypertrophic scars: JPMA. 2014; 64:1003.
2. Perdanasari AT. Intralesional treatment of keloids. Arch Plast Surg. 2014;41:620-9.
3. Bijlard E, Steltenpool S, Niessen FB. 5-FU in keloid treatment: a systematic review. Acta Derm Venereol. 2015;95(7):778–82.
4. Niessen FB, Spauwen PH, Schalkwijk J, Kon M. On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg. 1999;104:1435–58.
5. Mustoe TA, Cooter RD, Gold MH, Hobbs FD, Ramelet AA, Shakespeare PG, et al. International clinical recommendations on scar management. Plast Reconstr Surg. 2002;110: 560–71.
6. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med. 2011;17: 113-25.
7. Gauglitz GG, Kunte C. Recommendations for the Prevention and Therapy of Hypertrophic Scars and Keloids. Hautarzt. 2011;62:337-46
8. Sharma S, Bassi R, Gupta A. Treatment of small keloids with intralesional 5-fluorouracil alone vs. intralesional triamcinolone acetonide with 5-fluorouracil. J Pak Assoc Dermatol. 2012; 22:35-40
9. Shah VV, Aldahan AS, Mlacker S, Alsaidan M, Samarkandy S, Nouri K. 5-fluorouracil in the treatment of keloids and hypertrophic scars: a comprehensive review of the literature. Dermatol Ther (Heidelb). 2016;6:169–83.
10. Álvarez P, Marchal JA, Boulaiz H, Carrillo E, Vélez C, Rodríguez-Serrano F. 5-Fluorouracil derivatives: a patent review. Expert Opin Therapeut Pat. 2012;22:107–23.
11. Asilian A, Darougheh A, Shariati F. New combination of triamcinolone, 5-fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars. Dermatol Surg. 2006;32: 907-15.
12. Darougheh A, Asilian A, Shariati F. Intralesional triamcinolone alone or in combination with 5-fluorouracilfor the treatment of keloid and hypertrophic scars. Clin Experimental Dermatol. 2009;34:219-23.
13. Khalid FA, Mehrose MY, Saleem M, Yousaf MA, Mujahid AM, Rehman SU, et al. Comparison of efficacy and safety of intralesional triamcinolone and combination of triamcinolone with 5-fluorouracil in the treatment of keloids and hypertrophic scars: Randomized control trial. Burns. 2019;45(1):69-75.
14. Hochman B, Locali RF, Matsuoka PK. Intralesional triamcinolone acetonide for keloid treatment: a systematic review. Aesthetic Plast Surg. 2008;32:705–9.
15. Ren Y, Zhou X, Wei Z, Lin W, Fan B, Feng S. Efficacy and safety of triamcinolone acetonide alone and in combination with 5-fluorouracil for treating hypertrophic scars and keloids: a systematic review and meta-analysis. Int Wound J. 2016;14(3):480-7.
16. Jiang ZY[1], Liao XC, Liu MZ, Fu ZH, Min DH, Yu XT, Guo GH. Efficacy and safety of Intralesional Triamcinolone Versus Combination of Triamcinolone with 5-Fluorouracil in the Treatment of Keloids and Hypertrophic Scars: A Systematic Review and Meta-analysis. Aesthetic Plast Surg. 2020 Apr 27. Doi: 10.1007/s00266-020-01721-2. [Epub ahead of print].
17. Sharma S, Bassi R, Gupta A. Treatment of small keloids with intralesional 5- fluorouracil alone vs. intralesional triamcinolone acetonide with 5-fluorouracil. J Pak Assoc Dermatol. 2012;22:35-40.
18. Davison SP, Dayan JH, Clemens MW, Sonni S, Wang A, Crane A. Efficacy of intralesional 5-fluorouracil and triamcinolone in the treatment of keloids. Aesthet Surg J. 2009;29:40-6.
19. Tandon H, Kumar A, Rathore PK. Comparative study of efficacy and safety of intralesional triamcinolone acetonide versus intralesional 5-fluorouracil versus combination of both in management of keloids: a randomized control trial. Global J Res Analysis.

2019;8(12):38-40.
20. Reddy CVPK, Surekha A. A comparative study on treatment of keloid with triamcinolone versus 5-fluorouracil and triamcinolone. Int Surg J. 2020;7(5):1373-7.
21. Srivastava S, Patil A, Prakash C, Kumari H. Comparison of intralesional triamcinolone acetonide, 5-fluorouracil, and their combination in treatment of keloids. World J Plast Surg. 2018;7(2):212-9.
22. Donkor P. Head and neck keloid: treatment by core excision and delayed intralesional injection of steroid. J Oral Maxillofac Surg. 2007;65:1292–6.
23. Bollero D, Malvasio V, Catalano F, Stella M. Negative pressure surgical management after pathological scar surgical excision: a first report. Int Wound J. 2015;12:17-21.
24. Urioste SS, Arndt KA, Dover JS. Keloids and hypertrophic scars: review and treatment strategies. Semin Cutan Med Surg 1999;18:159–71.