A Comparative Study of Intra Lesional Triamcinolone Acetonide alone and Triamcinolone Acetonide Combined with 5-Flourouracil in the Treatment of Keloids

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ABSTRACT

Introduction: Keloids are an excessive proliferation of dermal fibroblasts, spontaneously or following a skin injury, and are difficult to treat. Inspite of different modalities of treatment available, effective management of keloids is a distant dream. Study objective was to compare the use of intralesional triamcinolone acetonide and its combination with 5- fluorouracil in the treatment of keloid in terms of reduction in initial height of the scar.

Materials and methods: The randomised controlled trial was conducted at the Department of Dermatology Venerology and Leprosy, Osmania General Hospital, Hyderabad, from November 2017 to April 2018. It comprised patients of both genders having keloids (1cm to 5cm in size) with no history of treatment in preceding 6 months.

Those who were pregnant, planning pregnancy or lactating were excluded from the study. The subjects were divided into two groups: Group A received intralesional triamcinolone acetonide alone; and Group B received triamcinolone acetonide + 5-flourouracil. Eight injections were given at 3 weekly interval. Scars were assessed 4 weeks after the completion of treatment on a five-point scale. SPSS 16 was used for statistical analysis.

Results: The 80 subjects in the study were divided into two equal groups of 40(50%) each. Good to excellent results were seen in 27(67.5%) cases in Group A compared to 34(85%) in Group B.

Conclusion: Combination of triamcinolone acetonide and 5-flourouracil is superior to triamcinolone acetonide therapy in the treatment of keloids.

Keywords: Keloids, Triamcinolone Acetonide, And 5-Flourouracil.

INTRODUCTION

Keloids – word derived from Greek word chele = crab's claw, oid = like describing the lateral growth of tissue into unaffected skin.[1] Keloids are formed as a result of an overgrowth of fibrous tissue following a minor trauma such as vaccination, ear piercing. However spontaneous keloids may even arise without any history of trauma in genetically susceptible individuals.[2] They occur most commonly on the chest, shoulders, upper back, neck and earlobes.[3] Ear lobe keloid can assume several clinical forms and is more destructive lesion when the whole lobe is involved.[4] These scars have been shown to exist in hypermetabolic state.

Effective treatment of keloid has been a constant disappointment and distant dream inspite of many recent modalities of treatment being tried, but none of them either single or in combination gave promising results when used.[5] Intralesional Triamcinolone acetonide (TAC) is the most commonly used corticosteroid in the management of keloids, it suppresses the inflammatory process, diminishes collagen and glycosaminoglycan synthesis, inhibits fibroblast growth factors. It also enhances collagen and fibroblast degeneration.[6]

5-fluorouracil (5-FU) is a fluorinated pyramidine, an antimetabolite, inhibits thymidylate synthase and interferes with RNA synthesis and function. It blocks collagen synthesis and fibroblast proliferation.[7]

The main aim of this study was to assess the efficacy of intralesional TAC+5-FU over TAC alone so that a better treatment modality can be recommended to treat keloids.

MATERIAL AND METHODS

This was a randomized controlled trial conducted at the Department of Dermatology Venerology and Leprosy, OGH, Hyderabad, Telangana, from November 2017 to April 2018. The sample size of 80 cases was taken.

Patients having keloids presented to out patient Department of dermatology of both genders, age between 15 -50years, irrespective of size and site of the keloid, with no prior treatment history in past 6 months were included in the study. Pregnant and lactating mothers and those who were planning pregnancy and those with other comorbidities were excluded from the study. The sample size of 80 was randomized in to two groups. Group A – 40 patients treated with intralesional triamcinolone acetonide and Group – B 40 patients treated with combination of intralesional triamcinolone acetonide and 5 – fluorouracil. Patients were divided into these groups by a randomization coding system derived from a computer-

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generated randomization table. Written informed consent was taken. Details of the patients, like name, age, sex, address, family history, presenting complaints, and history related to the keloid were recorded.

Keloids in Group A received intralesional triamcinolone acetonide (TAC) 40 mg/ml, keloids in Group B received intralesional injection of a combination of TAC (40mg/ml) and 5FU (50mg/ml) in a ratio of 1:9. The drugs used were undiluted except for the said combination.

Injections were made with 27G insulin syringe such that volume injected did not exceed 0.5 ml per square centimetre of keloid. Whenever necessary, multiple pricks were made 1 cm apart to ensure complete and uniform distribution. A maximum of 2 ml was injected per session. Injections were administered every 3 weeks till 24 weeks. No local infiltration of anaesthetics was done. Patients received no other therapies like scar massage, laser therapy or pressure garments during the course of study.

All patients were evaluated prior to every injection and a final evaluation was performed 28 weeks after first dose. Evaluation was done objectively using Vancouver Scar Scale (VSS) and subjectively by assessing pain and pruritus. Adverse effects at the time of injection and other complaints during the course of treatment were also recorded.

VSS was originally designed by Sullivan et al to assess burn scars which has since been extended to include other scars as well,. For VSS, keloid height was measured with callipers; pliability was assessed by palpation; vascularity was assessed by visual inspection; pigmentation was scored after blanching and comparing it with the surrounding skin. Pain and pruritus were scored on a 3-point scale as follows: 0=no pain/pruritus; 1=mild; 2=moderate; 3=severe pain/pruritus.

Variable	TAC	T + F
Mean age (years)	23.45	26.34
Sex (%)		
Female	24 (30)	24 (30)
Male	16 (20)	16(20)

Table-1: Age and sex distribution

Etiology (%)	TAC	T + F
Trauma	26 (32.5)	24 (30)
Infections	8 (10)	8 (10)
Spontaneous	6(7.5)	8 (10)

Table-2: Etiological distribution

Anatomical location (%)	TAC	T + F
Pre sternum	16 (20)	18 (22.5)
Trunk	12 (15)	10 (12.5)
Extremities	8 (10)	8 (10)
Face	4 (5)	4 (5)

Table-3: Distribution based on anatomy

RESULTS

A total of 80 patients completed the study. The youngest patient included in the study was 18 and the eldest was 50 years old. There were 40 females and 40 males in the study. Trauma etiology (n=50) was the commonest followed by infective (n=16) and spontaneous (n=14). Presternal region (n=34) was the most frequently involved region, followed by trunk (n=32), extremities (n=16), and face(n=8). The base line characteristics in terms of age, sex, etiology and region involved were comparable in all three groups. (Tables 1,2 and 3).

Mean preinjection VSS scores for all treatment groups at every evaluation Baseline And During Treatment are presented in Table 4. There was reduction in height, vascularity and pliability and pigmentation at every successive assessment in all three groups which was maintained till the final evaluation. There was no significant difference in baseline pre-injection scores of pain and pruritis and all parameters of VSS (Table 4).

Comparison using wilcoxon test showed that improvement in terms of height, vascularity and pliability was fastest with TAC +5FU than that of TAC alone, which was statistically significant.

Decrease in pigmentation was faster with TAC+5-FU

Parameters	Group	0 Week	6 Weeks	12 Weeks	18 Weeks	24 Weeks
Height	TAC	1.8 ± 0.58	1.7 ± 0.48	1.4 ± 0.52	1.3 ± 0.66	0.63 ± 0.41
	T + F	1.88 ± 0.41	1.67 ± 0.33	1.3 ± 0.53	0.91 ± 0.41	0.35 ± 0.32
Vascularity	TAC	1.78±0.36	1.64 ± 0.33	1.33 ± 0.25	0.8 ± 0.11	0.3 ± 0.1
	T + F	1.8 ±0.23	1.5 ± 0.6	1.1 ± 0.23	0.8 ± 31	0.27 ± 0.34
Pliability	TAC	2.4 ± 0.44	2 ± 0.45	1.78 ± 0.39	1.1 ± 0.21	0.7 ± 0.3
	T + F	2.7 ± 0.61	2 ± 0.54	1.5 ± 0.8	0.9 ± 0.51	0.41 ± 0.23
Pigmentation	TAC	1.99 ± 0.72	1.71 ± 0.51	1.51 ± 0.5	1.3 ± 0.41	0.8 ± 0.58
	T + F	1.78± 0.37	1.5 ± 0.47	1.12 ± 0.68	0.9 ± 0.27	0.31 ± 0.24

Table-4: Mean vancouver scar scale score baseline and during treatment

	Group	0 Week	6 Weeks	12 Weeks	18 Weeks	24 Weeks
Pain	TAC	2.32	1.8	0.56	0.35	0
	T + F	2.45	1.5	0.45	0.31	0
Pruritus	TAC	2.66	2.3	1.63	1.1	0.4
	T + F	2.7	2.15	1.38	0.82	0.31

Table-5: Mean injection scores for subjective parameters baseline and during treatment

Adverse effect	Treatment group	
	TAC	TAC+5-FU
Telangiectasia	3	1
Atrophy	4	2
Ulcers	0	4
Systemic adverse effects	0	0

Table-6: Summary of adverse effects.

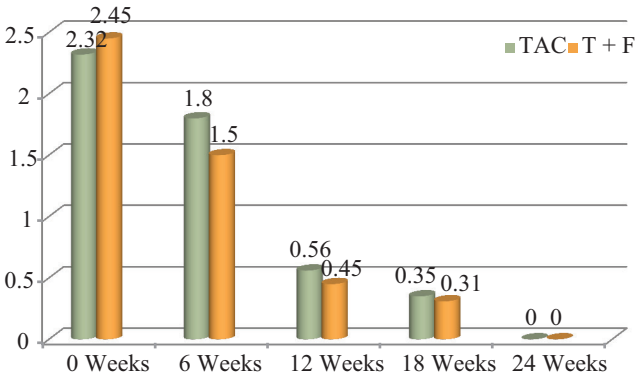

Chart-1: Mean Injection Scores For Pain

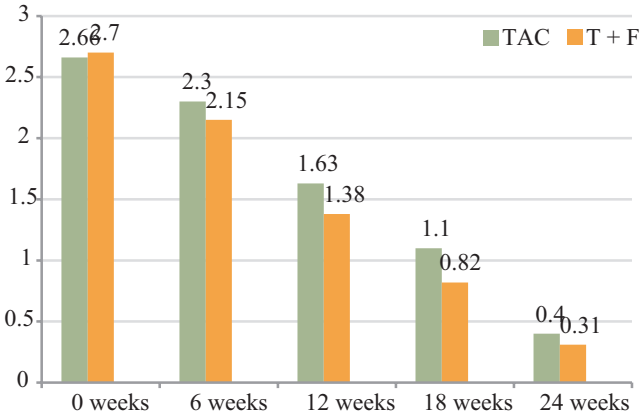

Chart-2: Mean Injection Scores For Pruritus

than TAC alone was highly significant. Pain and pruritus consistently reduced at every successive assessment but the difference in reduction of pain was not significant. Reduction in pruritus, however, was significantly faster with TAC+5-FU.

Telangiectasias and skin atrophy were seen most frequently in TAC group and skin ulceration in TAC + 5-FU group which was not seen in TAC group. Systemic adverse effects in the form of anemia, leukopenia or thrombocytopenia were not noted in any patient. No other abnormalities were noted in any other blood investigations. A summary of adverse effects observed in all groups is summarised in Table 6. Pain at injection site was a common problem in TAC+5-FU group compared to that of TAC group.

DISCUSSION

Keloid is basically a disease of the young. Most common in people younger than 30 years with equal sex distribution. Its occurence is also influenced by elevated hormone levels, especially during puberty and pregnancy. Because of significant psychological and functional burden, patients frequently seek medical treatment. Inspite of availability of wide modalities of treatments, TAC is most commonly used. TAC is one of the most commonly used corticosteroids with a dose of 40mg/ml given at 3 weekly interval over a period of 24 weeks. Despite the fact that intralesional TAC has shown 50% to 100% clinical efficacy, the result has not been satisfactory.[8] Moreover, usage of TAC is associated with various unpleasant effects such as atrophy, telangiectasia, and pigmentary changes, which are not desirable for majority of the patients.[9]

5-FU is a fluorinated pyramidine, an antimetabolite, which inhibits thymidylate synthase and interferes with RNA synthesis ad function. Recent evidence shows that it blocks collagen synthesis and blocks fibroblast proliferation in keloids.[10] It is usually given in the dose of 50mg/ml intralesionally weekly or fortnightly. Intralesional 5-FU is safe, provided the recommended upper limit of dose is not breached. Side effects like erythema and ulceration are common when pure 5-FU is used. In the current study 45mg of 5-FU (0.9ml) was mixed with 4mg TAC (0.1 ml). This combination is documented as more effective and gives rapid response with fewer side effects.[11]

Thorough search of literature regarding the use of corticosteroids in the management of keloids reveals that a dose of 10 – 40mg/ml TAC is effective. The concentration of TAC would be 4mg/ml in a mixture of TAC and 5-FU. This concentration would not have any effect on reducing the size of the keloid but it reduces 5-FU induced inflammation.

The combination regimen has been proven to be better than TAC alone.[12] A recent meta-analysis by Ren et al concluded that TAC+5FU is safer and more efficacious than TAC alone. Studies have also shown the effectiveness of the combination to be significantly better than 5FU.[13] But all these studies cannot be directly compared to each other due to lack of standardization. We have attempted standardizing the comparison by using an accepted scar assessment scale. Even so, these objective parameters are observer dependent and prone to errors. Evaluation by the same independent trained observers, such as in our study, can help minimize this error. We also added a dimension of subjective assessment since keloids are ultimately more of a subjective concern for the patient.

In our study, that by using a combination of TAC+5-FU resulted in more than 50% improvement in about 80% of patients. In comparison with TAC group it looks as if TAC=5-FU combination is more effective and faster response with fewer if not without any side effects. No systemic adverse effects of 5FU were noted in the study.

A limitation of the current study is the short duration of follow-up. All patients in our study were observed for 28 weeks, during which there was no recurrence. A long-term follow-up in such a prospective study is difficult; our interaction with such patients leads us to believe that this is probably because the patient is unwilling to return when he is convinced that his 'disease' has been apparently 'cured'. Perhaps a longer prospective study focusing on recurrence might prove more useful in this regard.

CONCLUSION

The present randomised controlled comparative study has shown that combination therapy of TAC+5-FU is more efficacious and faster in response with fewer side effects compared to TAC alone in the treatment of keloids.

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