Treatment of small keloids with intralesional 5-fluorouracil alone vs. intralesional triamcinolone acetonide with 5-fluorouracil

Saurabh Sharma*, Roopam Bassi**, Amit Gupta***

*Department of Dermatology & Venereology, Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar, India.
**Department of Physiology, Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar, India.
***Consultant Dermatologist, Hoshiarpur, India

Abstract

Background Keloid is a benign well demarcated area of dense, fibrous tissue overgrowth that extends beyond the original defect.

Objective To compare the efficacy of intralesional 5-fluorouracil (5-FU) alone vs. intralesional triamcinolone acetonide (TAC) in combination with 5-fluorouracil.

Patients and methods Study on 50 clinically diagnosed lesions of keloids from 28 patients was conducted. In group A, 25 keloid lesions were subjected to 50 mg/ml 5-FU intralesionally while in group B, 25 keloid lesions were injected intralesionally with a combination of 40 mg/ml triamcinolone acetonide (0.1 ml) and 5-FU 50mg/ml (0.9 ml). Both the procedures were repeated at weekly intervals for 4 weeks, then bimonthly for 2 months and then monthly until the keloid lesions in both groups virtually assumed the same level as that of surrounding tissue or for a maximum of 3 months.

Results Good to excellent response was seen in 96% cases in group B in contrast to 72% cases only in group A. The group B lesions showed better improvement than group A lesions in pruritus, pain, tenderness, restriction of movements and cosmetic problem. No recurrence was seen in any of the lesions.

Conclusion The combination of 5-FU and triamcinolone acetonide is a better modality of treatment of small keloids compared with 5-FU alone.

Key words Keloid, 5-FU, triamcinolone acetonide.

Introduction

A keloid is benign hyperproliferative growth of dermal fibroblasts which extends beyond the borders of original wound, does not regress spontaneously and tends to recur after excision.¹ Hypertrophic scars and keloids may lead to significant morbidity as well as pruritus, pain, restriction of motion, or cosmetic disfigurement.² Various therapeutic modalities like drugs, compression therapy, laser therapy, surgical excision, 5-fluorouracil, radiotherapy, silastic gel sheet, intralesional corticosteroids,
cryosurgery etc. have been advocated for the treatment of keloids without convincing results.

Till date, keloid poses a challenge to the dermatologists due to its ability to recur in spite of adequate treatment and variable response to different therapies available. Both softening and flattening of keloids have been attained by intralesional corticosteroid therapy. Some promise in the treatment of keloids has been offered by 5-FU. The mode of action of this modality is by interfering with pyrimidine metabolism and converting to 5-fluoro-2'-deoxyuridine-5'-phosphate (F-dUMP), which is a potent inhibitor of thymidylate synthetase, thus DNA synthesis is blocked. Triamcinolone acetonide acts by inhibiting protein synthesis and fibroblast migration. It also enhances degradation of collagen. We have observed favorable results of keloid regression by the combined action of intralesional 5-FU and triamcinolone acetonide. It has been difficult to assess the efficacy of the existing treatment modalities because there have been limited number of controlled, comparative studies of the effectiveness of various treatment methods in improving the appearance or symptoms of these scars. The following method employed in this study is presented to emphasize the concept of combining intralesional 5-FU and triamcinolone acetonide in the management of keloids.

**Patients and methods**

28 patients (16 males and 12 females) with 50 clinically diagnosed lesions of intractable keloids (<5x5x0.5 cm³) visiting Dermatology and Venereology Outpatient Department (OPD) of Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar were enrolled for the study from August 2007 to July 2009 after taking their written consent. The lesions were randomized into two groups according to side of body involved, which was divided by a midsagittal line: the lesions present over the left side of the body were labelled as group A, whereas the lesions present over the right side of the body were labelled as group B. Patients with age below 20 years and above 60 years were not included in the study. It was ensured that all the 50 lesions selected were keloids, that none showed a tendency to flatten spontaneously nor had undergone any previous treatment and all showed extension beyond the site of original injury. A detailed medical history of each patient was taken with special emphasis on duration of illness and initial injury giving rise to keloid formation. In addition, complete general physical and mucocutaneous examination was performed. Investigations like hemoglobin, total leukocyte count, differential leukocyte count and urine complete examination were done in each case.

The 50 keloid lesions were equally divided into 2 groups A and B according to above criterion. Group A 25 keloid lesions were subjected to 50 mg/ml 5-FU intralesionally by a 27 gauge insulin syringe. In group B 25 keloid lesions, in addition to 5-FU 50mg/ml (0.9 ml), 40 mg/ml triamcinolone acetonide (0.1 ml) was injected intralesionally by a 27 gauge insulin syringe, i.e. a concentration ratio of 9:1 was taken. 0.1 ml of each of the solutions were injected 1 cm apart in lesions of each group. In both the groups, the patients were kept under observation for next 20 minutes for immediate complications like pain, edema, erythema and bullae formation. Thereafter, the patients were advised to go home and report for check up after 48 hours. The duration of treatment given was limited to 6 months where both the procedures were repeated at weekly intervals for 4 weeks, then bimonthly for 2 months and then monthly until the keloid lesions in both groups assumed virtually the
same level as that of surrounding tissue or for a maximum of 3 months. Every time, lesions were examined regarding their pain, edema, bullae formation, ulceration, secondary infection, pigmentary changes, flatness and recurrence. Before and after photographs of lesions were taken of each patient after noting the dimensions of every lesion with the help of calipers. At the end of study period, the response to treatment in terms of flattening of the lesions was categorized as excellent: 76-100% improvement; good: 51-75% improvement; fair: 26-50% improvement; and poor: <25% improvement. All the patients were followed up for 12 months to note the recurrence of lesions. The results achieved were recorded on the prescribed pro forma and subjected to relevant statistical analysis at the end of the study.

Results

The results were evaluated primarily on the basis of improvement in signs and symptoms, flattening of lesions, recurrence and prolonged side-effects after the completion of treatment. The immediate local complications seen in almost every patient were pain, edema, purpura, hyperpigmentation and stinging sensation. The group B lesions showed better improvement than group A lesions in pain, tenderness, restriction of movements, and cosmetic problem. The difference was statistically significant as regards to improvement in pruritus (Table 1).

Table 2 shows that the response to treatment in group B lesions was definitely much better than the response to treatment in group A lesions. Good to excellent response was seen in 96% cases in group B in contrast to 72% cases only in group A.

In addition, only 4% of the patients gave poor or fair response to the treatment in group B compared with 28% in group A. Therefore, the treatment applied in group B proved to be better than the treatment response in group A.

Table 3 compares the side effects in both groups. Out of 25 keloid lesions in group A, 2 (8.0%) lesions showed atrophy, 1 (4.0%) lesion showed hyperpigmentation, 1 (4.0%) lesion showed hypopigmentation and no lesion showed

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<thead>
<tr>
<th>Table 1 Keloid lesions showing comparison of improvement in signs and symptoms in both the study groups.</th>
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<td>Signs and symptoms</td>
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<tr>
<td>Cosmetic problem</td>
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<td>Pruritus</td>
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<td>Restricted movement</td>
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<td>Pain</td>
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<td>Tenderness</td>
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<th>Table 2 Keloid lesions showing comparison of type of response at the completion of treatment in both the study groups.</th>
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<td>Flattening of lesions</td>
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<tr>
<td>76-100%</td>
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<td>51-75%</td>
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<td>26-50%</td>
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<td>1-25%</td>
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<td>Total</td>
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X² = 5.357; df = 1; p = 0.020 (Significant)
Table 3 Keloid lesions showing comparison of delayed adverse effects in both the study groups

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<thead>
<tr>
<th>Delayed adverse effects</th>
<th>Group A</th>
<th>Group B</th>
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<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>Atrophy</td>
<td>2 (8)</td>
<td>3 (12)</td>
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<tr>
<td>Hyperpigmentation</td>
<td>1 (4)</td>
<td>1 (4)</td>
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<tr>
<td>Hypopigmentation</td>
<td>1 (4)</td>
<td>2 (8)</td>
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<tr>
<td>Telangiectasia</td>
<td>-</td>
<td>1 (4)</td>
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telangiectasia after the completion of treatment. In group B, 3 (12.0%) lesions showed atrophy, 1 (4.0%) lesion showed hyperpigmentation, 2 (8.0%) lesions showed hypopigmentation and 1 (4.0%) lesion showed telangiectasia after the completion of treatment. These effects were found to be reversible during the follow up period of 12 months. No systemic adverse effects (e.g. anemia, leucopenia, thrombocytopenia) occurred in this study. At the end of follow up of 12 months, 21 patients (84%) in group A and 19 patients (76%) in group B reported back to us. No recurrence was seen in any of the lesions.

Discussion

Keloid is an abnormal disfiguring scar with claw like extensions in the normal skin. It becomes raised and thickened within 3-4 weeks of the provocative stimulus. The lesion becomes firm and pink or red plaque which may grow for months or years. The surface of a keloid becomes smoother and rounder and extends beyond the area of original lesion. It is often irritable, hypersensitive and sometimes tender. Various techniques had been tried in the past to find a possible solution to this puzzling state of keloids but none has provided us with dependable results. The present study has been conducted to compare the efficacy of intrallesional 5-FU versus combination of intrallesional triamcinolone acetonide (TAC) and 5-FU in the treatment of small keloids (<5x5x0.5cm³). We found that combination therapy with intrallesional TAC and 5-FU was an effective treatment for keloids in a controlled comparative study. The results achieved were much better than with intrallesional 5-FU injections alone. To our knowledge, not much work has been done worldwide to compare these two treatment modalities.

Intrallesional 5-FU acts by inhibiting fibroblast proliferation and has antimetabolite activity. It also has an inhibitory effect on TGF-β-induced expression of the type I collagen gene in human fibroblasts. It interrupts both DNA and RNA synthesis at several levels, including the inhibition of thymidylate synthetase and the production of toxic metabolites. Intrallesional TAC causes inhibition of protein synthesis and fibroblast migration. It also enhances degradation of collagen. Steroids are known to inhibit collagen synthesis and possess anti-inflammatory properties. Atrophy, one of the side effects of steroids, is utilized to achieve therapeutic effect in keloids. Addition of 0.1 ml of triamcinolone acetonide (40 mg/ml) to 0.9 ml of 5-FU (50 mg/ml) helps to reduce the pain and also the inflammation. It has been reported that 5-FU delivered intrallesionally once weekly or once every 2 weeks to keloids and hypertrophic scars is effective.

The only immediate side effects seen with 5-FU injections in both groups were pain, stinging sensation, purpura at injection site, and occasionally superficial ulceration. Hyperpigmentation was a constant feature seen in every case as was reported in other studies. The combined use of intrallesional TAC and 5-FU in the treatment of inflamed hypertrophic scars has previously been reported to be effective and can avoid these potential complications. Transient burning sensation or pain was the most common immediate adverse effect reported by all patients at the TAC+5-FU-
and 5-FU-treated segments which is consistent with other studies.\textsuperscript{2,11,13,14}

The major response in flattening was seen in both the groups after 12 weeks. We found that the type of response to treatment in terms of flattening in group B lesions was statistically significant as compared to group A lesions (Table 2). In group A, good to excellent response was seen in 72\% lesions. This is in accordance with the study conducted by Nanda and Reddy.\textsuperscript{14} In our study, excellent response was seen in 32\% of lesions while poor response was seen in 12\% of lesions. These results are almost consistent with another study.\textsuperscript{11} However, our results are in variance with few other studies.\textsuperscript{12,13,15} In group B, good to excellent response was seen in 96\% lesions. Our results are consistent with the study by Wu et al.\textsuperscript{16} which showed an efficacy of 97.14\%. The results of our study are comparable with those reported previously\textsuperscript{17} where average size reduction was 84\%. However, our results are in variance with other studies\textsuperscript{15,18} where duration of treatment was just 8 weeks.

At the end of present study, 2(8\%) lesions developed atrophy while no lesion developed telangiectasia in group A. Our results are almost similar with previously conducted studies\textsuperscript{2,14} which also did not observe atrophy and telangiectasia. We also observed hyperpigmentation and hypopigmentation in 1 (4\%) lesion each in the same group. In group B 25 keloid lesions, 3 (12.0\%) lesions showed atrophy, 2 (8.0\%) lesions showed hypopigmentation, 1 (4.0\%) lesion showed hyperpigmentation and 1 (4.0\%) lesion showed telangiectasia after the completion of treatment. These effects were found to be reversible during the follow up period of 12 months. Although, we used a higher dose of triamcinolone acetonide, i.e. 40 mg/ml in our study as compared to dosage used by Fitzpatrick,\textsuperscript{2} i.e. 10 mg/ml, yet we did not find any significant local adverse effects of steroids due to the repetition of the procedures at varying intervals rather than performing every time at weekly intervals as in most other studies.\textsuperscript{2,18} Similar to the results of other studies,\textsuperscript{11,14,18} we found that at the end of our study, there were no serious systemic side-effects or any difference in peripheral blood counts in both the groups.

No recurrence in any of the lesions of both the groups was reported at the end of the follow up period of 12 months as was seen in other studies.\textsuperscript{11,14} We also observed a correlation between the size of keloids and duration of keloids with the duration of treatment in our study. The keloids which were smaller in size and were of shorter duration, responded better than the other lesions.

**Conclusion**

The combination of 5-FU and TAC has a synergistic effect on keloids. Although satisfactory improvement was seen in both the comparison groups, it was more significant and acceptable to the patients in the 5-FU+TAC group. We suggest that the treatment should be individualized depending upon the size, thickness, distribution, and duration of the lesions.

**Study limitation**

Our study consisted of fifty keloid lesions. We suggest some more randomized clinical trials with a greater sample size.

**References**

1. Kelly AP. Medical and surgical therapies for keloids. *Dermatol Ther* 2004;\textsuperscript{17}212-18.


