Indian J Surg (July–August 2012) 74(4):326–329
DOI 10.1007/s12262-011-0399-y

A Comparative Clinical Study on Role of 5-Flurouracil Versus Triamcinolone in the Treatment of Keloids

Anil K. Saha · Madhumita Mukhopadhyay

Received: 12 April 2011 / Accepted: 21 December 2011 / Published online: 10 January 2012

Abstract A wide range of therapies exist for keloids. But despite the multiple treatment modalities available, keloids still remain a significant challenge for both the clinician and the patient. To compare the efficacy of 5-flurouracil (5-FU) versus triamcinolone as a therapeutic agent for the treatment of keloids. A randomized control trial was carried out at a teaching hospital in Kolkata over a period 2.5 years. Forty-four patients took part in the study, 20 in group F and 24 in group T. The age ranged from 16 to 66 years. The mean age of group F was 34.7±11.0124 years (range 16–66 years) and of group T was 32.96±9.584 years (range 19–60 years). The difference in the age and sex between the two groups was comparable and not statistically significant (p=0.096). The response was rated as excellent (76–100% decrease in volume), good (51–75%), fair (26–50%), and poor (less than 25%). The reduction in keloid volume was comparable in both the groups. But side effects were much more in group F compared to group T. About 95% of the patients in group F found the injection very painful. About 6% of the patients in group F presented soon after the first two to three sessions with superficial ulcerations at the injection site accompanied by mild discomfort and discharge. This side effect was not seen in group T. Regarding pain at the injection site and superficial ulceration, the difference between the two groups was found to be statistically significant (p<0.05). The patients treated with 5-FU experienced side effects such as hyperpigmentation, pain at the injection site, and superficial ulceration, which were statistically highly significant. It appears from this study that triamcinolone is a better tolerated and less toxic alternative to 5-FU in the management of keloids.

Keywords Keloid · 5-Flurouracil · Triamcinolone acetonide

A. K. Saha (✉) · M. Mukhopadhyay
Calcutta National Medical College and Hospital,
Kolkata, West Bengal, India
e-mail: sahaanil64@yahoo.com

A. K. Saha · M. Mukhopadhyay
Block-II, 7A, Ekta Heights, 56, Raja S.C. Mallick Road,
Kollkata 700032, India

Introduction

Keloids are benign cutaneous lesions that are produced by uncontrolled synthesis and deposition of dermal collagen in predisposed individuals [1]. Clinically, they are firm nodules, which can be skin colored, hypopigmented, or erythematous secondary to telangiectasias. A wide range of therapies exist for keloids, with the commonly used modalities being intralesional steroid injection, surgical excision, cryotherapy, laser therapy, radiation therapy, and the application of silicon gel sheets. Other treatments that have been used with variable success rates include imiquimod, 5-flurouracil (5-FU), bleomycin, retinoids, calcium channel blockers, mitomycin C, and interferon-α2b [2]. Intralesional steroid injection is by far the most commonly used mode of therapy for keloids. Overall, this modality has a high degree of tolerability as well as effectiveness in reducing symptoms. Several studies evaluating intralesional steroids have reported roughly a 50% recurrence rate [2, 3]. In the recent past, intralesional 5-FU has been tried in hypertrophic scars and keloids in combination or as an individual therapeutic agent [1, 4–6]. A paucity of literature is available regarding the usefulness and safety profile of 5-FU as an individual therapeutic agent [1]. However, several studies suggest that the overall efficacy is not better than other modalities and significant side effects such as ulceration and hyperpigmentation make topical 5-FU less appealing [1–5]. Hence, we conducted a prospective trial to compare the efficacy of 5-

FU versus triamcinolone as a therapeutic agent for the treatment of keloids.

Material and Methods

This randomized control trial was carried out at a teaching hospital in Kolkata, India, from June 2008 to December 2010. The patients were randomized into two study groups, group F and group T. The patients in group F were given 5-FU, and patients in group T were given triamcinolone acetonide. Both groups received injections at weekly intervals for a maximum period of 6 weeks. Initially 50 patients were enrolled in the study. Later, 6 patients were excluded either due to refusal of subsequent treatment or lost to follow up. So, only 44 patients with keloids completed the study.

All patients had full blood cell count along with renal and liver function tests checked before treatment as a baseline, and again after 1 month of commencement of treatment. Pregnant patients or patients planning pregnancy in the near future, patients with chronic renal failure, and those showing any abnormalities of liver function tests or full blood cell count were excluded from the study. Patients younger than 12 years were also excluded from the study.

Patients in group F were treated once weekly with intralesional 5-FU (50 mg/mL). The delivered dose was adjusted according to the extent of the lesions but did not exceed 100 mg/session (2 mL). The solution was injected into the body of the keloid using a 30-gauge needle attached to a 1 mL insulin syringe, until slight blanching was clinically visible. Only the indurated, firm portion of the keloid was treated by multiple injections separated by approximately 1 cm. Group T patients were treated with triamcinolone acetonide at a concentration of 40 mg/mL. The delivery dose was adjusted according to the extent of the lesion, but did not exceed 2 mL/session. Other methods of injection were similar to 5-FU.

The clinical evaluation was performed by the same observer throughout the treatment and follow-up periods. The lesions were assessed for (1) reduction in volume of the keloid based on objective assessment of the lesion (flattening, decrease in length and width), (2) presence of itch and pain, before and after treatment, and (3) side effects during and after treatment. Patients were followed up for 1 year after the end of the treatment protocol. Software used for the statistical calculations was Winpepi (version 10.5, April 22, 2010).

The study was approved by the "Medical Ethical Committee for Human Research" of our hospital. Informed consent was taken from all the patients. Patients were informed that 5-FU is primarily an anticancer agent. Before enrollment for the study, all patients were provided with a written informed consent meeting all local institutional requirements.

Table 1 Reduction of volume of keloid

Improvement	Group F (n=20)	Group T (n=24)	p value
Excellent	10%	12.5%	p=1.000
(76–100)%	n=2	n=3	
Good	55%	54.17%	p=1.000
(51–75)%	n=11	n=13	
Fair	20%	25%	p=0.974
(26–50)%	n=4	n=6	
Poor	15%	8.33%	p=0.800
Less than 25%	n=3	n=2	
No response	—	—	—

Results

Forty-four patients took part in the study, 20 in group F and 24 in group T. The age ranged from 16 to 66 years. The mean age of group F was 34.7±11.0124 years (range 16–66 years) and of group T was 32.96±9.584 years (range 19–60 years). The difference in the age and sex between the two groups was comparable and not statistically significant (p=0.096). Lesions varied in number (1–6) and size (1–7 cm) and involved mainly the upper aspect of the back (Fig. 1),

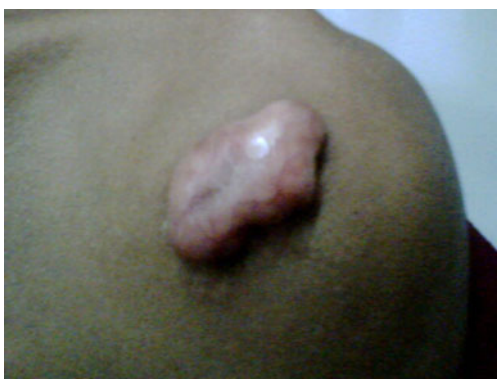

Fig. 1 Keloid at the upper part of the back

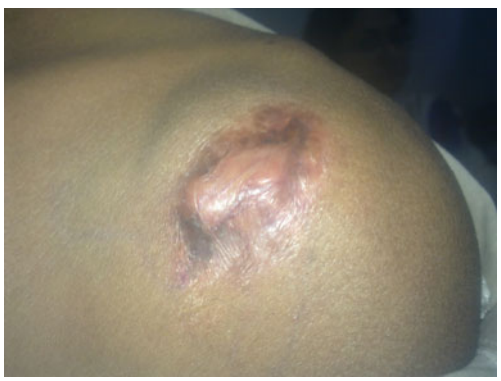

Fig. 2 Same keloid as in Fig. 1, showing fair response (26-50 %) to Triamcinolone acetate

Table 2 Other effects

Effects	Group F	Group T	*p* value
Hyperpigmentation	90%	12.5%	$p=0.000$
Reduction in pain	16.67%	66.67%	$p=0.06$
Reduction in itching	80%	79.17%	$p=1.000$
Pain at injection site	95%	4.17%	$p=0.000$
Superficial ulceration	65%	0%	$p=0.000$

chest, and arms. Itching was a constant symptom. In group F, 13 patients had a single lesion and 7 patients had multiple lesions. In group T, 14 patients had a single lesion and 10 patients had multiple lesions. The duration of the disease varied from 8 months to 20 years. If we consider duration of disease greater than 2 years to be long and 2 years and less to be short, then 12 out of 20 patients in group F and 10 out of 24 patients in group T had short duration of disease. Operations, acne, and burns were the major causes for the development of the abnormal scars.

The result of the different therapies on the volume of the keloid is given in Table 1. The response was rated as excellent (76–100% decrease in volume), good (51–75%) (Fig. 2), fair (26–50%), and poor (less than 25%). Treatment was discontinued once the therapeutic result was satisfactory. The average number of sessions needed in group F was five, whereas four sessions were needed in group T. Injection volumes ranged from 0.2 to 0.4 mL/cm^2 in both the groups. For both groups, the location and the number of lesions were not co-related to the therapeutic response. The therapeutic response was also not co-related with duration of the disease.

None of the patients showed failure to therapy. Softening and resolution of pruritus were the first clinical signs of improvement. Regression from the periphery was noted in all of the patients besides flattening of the lesions. The role of therapy on other aspects of the keloid including side effects is summarized in Table 2.

The reduction in keloid volume was comparable in both the groups. But the side effects were much more in group F

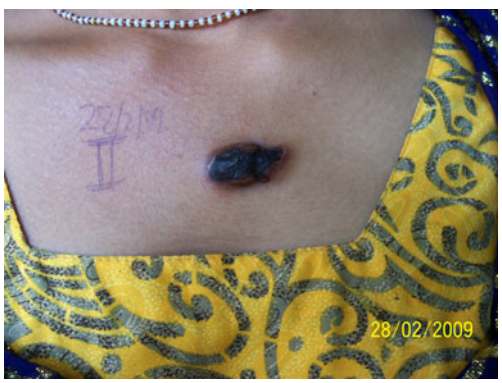

Fig. 3 Superficial ulceration with 5-FU treatment

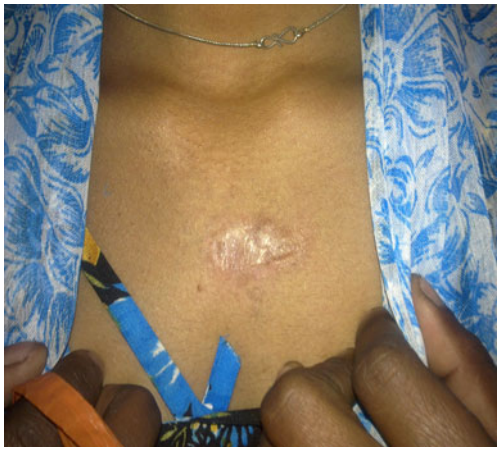

Fig. 4 Superficial ulceration resolved with topical Fusidic acid

compared to group T. About 95% of the patients in group F found the injection very painful. Occasionally, the pain was severe and persisted for 3–4 h after the injection. About 65% of the patients in group F presented soon after the first two to three sessions with superficial ulcerations at the injection site (Fig. 3) accompanied by mild discomfort and discharge. Ulceration healed with the use of topical 2% fusidic acid cream (Fig. 4). This side effect was not seen in group T. No hematologic side effects were noted in any of the patients. Regarding pain at the injection site and superficial ulceration, the difference between the two groups was found to be statistically significant ($p<0.05$).

All the patients were followed up for as long as 1 year or until recurrence was noted. In the 17 improved patients of group F, keloids recurred in 6 patients (35.29%) within 6 months of the last treatment. In 22 improved patients of group T, 8 patients (36.36%) had recurrence within 6 months of the last treatment. This was found to be statistically insignificant ($p>0.05$) (Table 3).

Discussion

A keloid may be defined as a benign growth of dense fibrous tissue developing from an abnormal healing response to a cutaneous injury, extending beyond the original borders of the wound or inflammatory response [2]. The common causes of these lesions are burn, surgery, and vaccination. These lesions are more prevalent in age from 10 to 30 years [7, 8]. For unknown reasons, keloids occur

Table 3 Recurrence rate

Group	Number of patients improved	Recurrence
Group F	17	6
Group T	22	8

more frequently among Blacks, Hispanics, and Asians and less commonly in Caucasians. Female predominance has been noted, but this may, in part, be reflected by the number of earlobe keloids secondary to piercing among women [2, 9]. Keloids occur most commonly on the chest, shoulders, upper back, back of the neck, and earlobes. Keloids are frequently symptomatic, with most patients reporting tenderness or pruritis [2].

On histologic examination, keloids are found to have increased collagen and glycosaminoglycan deposition, both major components of the extracellular matrix [10]. The collagen in keloids consists of thickened whorls of hyalinized collagen bundles in a haphazard array, known as keloidal collagen [11]. This is in contrast to normal scars where collagen bundles are oriented parallel to the skin surface.

Triamcinolone acetonide has been shown to inhibit collagen synthesis and fibroblast growth in vitro [12]. It has been reported that treatment of fibroblasts with triamcinolone acetonide results in a reduction in TGF-β expression and an increase in bFGF production. Intralesional steroid injection may be impractical for very large or multiple keloids since the pain of injection may be considerable and there is additional concern due to large doses of corticosteroids. The complications of intralesional steroids include skin atrophy, hypo- or hyperpigmentation, and the development of telangiectasias.

5-FU is a pyrimidine analog that is converted intracellularly into a substrate that causes inhibition of DNA synthesis by competing with uracil incorporation [13]. The increased rate of proliferation seen in keloidal fibroblasts suggests that 5-FU may be effective in limiting keloid growth [14]. A major drawback of systemic 5-FU is its association with anemia, leucopenia, and thrombocytopenia. Thus, even intralesional 5-FU should be avoided in pregnant and lactating women and patients with concurrent infections or bone marrow suppression [13].

In this study, we found that when keloid volume was considered, both modalities of treatment were equally effective, but the side effects were much more in case of 5-FU injection. Most of the patients in the 5-FU group found the injection very painful, and this was the cause of discontinuation of treatment in some patients. Ulceration and tissue sloughing were seen in 65% of the patients, which took a few weeks to heal. This has been observed in other studies also [1, 4–6]. None of these side effects were seen with triamcinolone acetonide injection, so the patient compliance was much more in the latter group. In our study , recurrence was seen in 35.29% of the improved patients in group F and in 36.36% of the improved patients in group T. Konchristopoulos et al. [4] reported 47% recurrence in the improved patients treated with 5-FU.

Despite their common occurrence and multiple treatment modalities available, keloids remain a significant challenge for both the clinician and the patient [2]. Considering the above facts, it appears that treatment for a benign disease like keloid with an anticancer drug like 5-FU does not give any special advantage over triamcinolone acetonide. The patients treated with 5-FU experienced side effects such as hyperpigmentation, pain at the injection site, and superficial ulceration, which were statistically highly significant. It appears from this study that triamcinolone is a better tolerated and less toxic alternative to 5-FU in the management of keloids. Based on emerging information on keloid pathophysiology, there is need for further studies in order to develop better therapies for pathologic scarring [2]. Intense research is underway to better understand the pathophysiology of the abnormal process leading to keloid formation. This will likely lead to more specific and effective treatments in the future.

References

1. Nanda S, Reddy BSN (2004) Intralesional 5-flurouracil as a treatment modality for keloids. Dermatol Surg 30(1):54–57
2. Robles DT, Moore E, Draznin M, Berg D (2007) Keloids: pathophysiology and management. Dermatol Online J 13(3):9
3. Kiil J (1977) Keloids treated with topical injections of triamcinolone acetonide (kenalog). Immediate and long-term results. Scand J Plast Reconstr Surg 11:169–172
4. Konchristopoulos G, Stefanaki C, Panaqiotopoulos A, Stefanaki K, Arqyrakos T, Petridis A et al (2005) Intralesional 5-flurouracil in the treatment of keloids: an open clinical and histopathologic study. J Am Acad Dermatol 52(3):474–479
5. Gupta S, Kalra A (2007) Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. Dermatology 204:13
6. Fitzpatrick RE (1999) Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg 5:224–320
7. Farahnaz FN, Jamshid N, Koroush A (2005) Comparison of therapeutic response of keloids and hypertrophic scars to cryotherapy plus intralesional steroid and bleomycin tattoo. Indian J Dermatol 50:129–132
8. Berman B, Beieley H (1995) Keloids. J Am Acad Dermatol 33:117–123
9. Kelly AP (2004) Medical and surgical therapies for keloids. Dermatol Ther 17:212–218
10. Berman B, Flores F (1998) The treatment of hypertrophic scars and keloids. Eur J Dermatol 8:591–595
11. Lee JY, Yang CC, Chao SC et al (2004) Histopathological differential diagnosis of keloid and hypertrophic scar. Am J Dermatopathol 26:379–384
12. Cruz NI, Korchin L (1994) Inhibition of human keloid fibroblast growth by isotretinoin and triamcinolone acetonide in vitro. Ann Plast Surg 33:401–405
13. Apikian M, Goodman G (2004) Intralesional 5-fluorouracil in the treatment of keloid scars. Australas J Dermatol 45:140–143
14. Uppal RS, Khan U, Kakar S et al (2001) The effects of a single dose of 5-fluorouracil on keloid scars: a clinical trial of timed wound irrigation after extralesional excision. Plast Reconstr Surg 108:1218–1224