

# Effects of Combined Intralesional 5-Fluorouracil and Topical Silicone in Prevention of Keloids: A Double Blind Randomized Clinical Trial Study

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**Abstract-** Keloids are aesthetically disfiguring and severely disabling. The optimal treatment remains undefined. This clinical study, evaluate the efficacy and side effects of combined topical silicone and 5-Fluorouracil on the prevention of keloids. In this double blind randomized clinical trial, fifty patients with keloids were randomly allocated in two groups. The control group were treated by perilesional surgical excision of keloids combined with topical silicone and the trial group were treated with adjuvant treatment of intralesional 5-Fluorouracil. All patients were examined and assessment was done by an independent observer. the data collected were analyzed by SPSS statistical software with using tables and  $\chi$  square tests. 75% of the cases in the trial group were keloid free 21% have keloid partially improvement and 4% have keloid recurrence, compared to patients in the control group respectively: 43%, 35% and 22%, findings suggest that efficacy of 5-Fluorouracil combined with topical silicone used for the prevention of keloid is comparable to other modality. The lack of any serious side effects and the evidence of recurrence at one year of follow-up make this an effective tool for the prevention of keloids.

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## Introduction

Keloid lesions are characterized by excessive benign cutaneous scarring that is a defective wound healing process. Keloids have also been referred to “kele” meaning crab pincers and “canceroids” meaning cancer-like or crab-like and “chelloids” meaning claw-like, because of their aggressive and expansive nature (1).

These are considered idiopathic excess accumulation of collagen in the wound by increasing biosynthesis of fibroblasts that the target of all therapeutic modalities is to suppress the uncontrolled fibroblast activity. They are arising from different skin lesions such as wounds, cuscations, hums, granulomas, acne, vaccination, aer-lobe piercings or spontaneously with no definable cause (2, 3). Although, the first line of treatment for keloids is surgery, medical therapy such as intralesional steroids, interferon, topical cyclosporine, retinoid, verapamil hydrochloride, topical silicone and physical approach such as pressure, cryotherapy, irradiation and laser therapy has been tried prevention of keloids still

presents a major dilemma (4,5). Intralesional 5-FU has been tried in hypertrophic scars and keloids in combination or as an individual therapeutic agent (6). The aim of this study was to determine the effectiveness of combination of 5-fluorouracil (5-FU), which inhibits fibroblasts proliferation both in vitro and in vivo, and topical silicone to prevent keloids (7-9).

## Patients and Methods

In this double blind randomized clinical trial study, fifty keloid patients, 30 females and 20 males, age range 22-45 years, with one or more keloids of varying size and duration who presented to the surgery out patient department in Shahid Beheshti Teaching Hospital in Yasuj, a city in Iran, during three years from September of 2004 to September of 2008, were included in the study. The include criteria for participant in study were: written informed consent, have not any renal and kidney failure based on laboratory result and clinical examination, and the exclude criteria for all patients

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was renal or liver disease in course of study. The selected patients were randomly allocated by ten randomized block design to two equal groups of 25 persons. Assessment experts and Patients were blind to assignments of patients to trial or control groups. Three patients were lost to follow in study one belongs to trial group that were excluded because of renal disease and two of control group one because of missing and other because of dead.

In respect to size and duration of keloid lesions are as follow: size (range 2-6 cm) and duration (range 2-5 years) in typical sites. Specifically, they presented 19 lesions as the sternal scars, 20 had back and abdomen and 5 had deltoid keloids.

In this study, keloid was defined as an itchy, raised, persistent growth that had irregular margins. A detailed history pertaining to the duration, any predisposing factors such as trauma, infection, or any inflammatory skin disorder, any prior treatment taken, and evidence of any systemic disease and family history were obtained in all the cases. In all patients, any prior treatment was discontinued at least one month before starting intralesional 5-FU and silicone therapy. Differential and total leukocyte counts, liver function tests and renal function test were performed in all of the patients at 0, 12, 20 and 48 weeks.

In the trial group, keloids were treated by surgical excision, topical silicon applied in sheets, intralesional 5-fluorouracil injections at timed intervals, the second group, and the controls, received the same treatment except that no 5-fluorouracil was administered. In both groups, the surgical excision of keloids was performed perilesionally, and topical silicon was applied at the first signs of scar formation (10-20 days) and lasted for 6-12 months. The first group received 50 mg/ml of 5-FU with

doses varying from 0.6-1 ml depending on size of keloid. We used the following treatment schedule: intralesional infiltrations on postsurgical days 7, 14, 28 and during the second and third months. This was always followed by application of silicon sheets. All patients were examined and Assessment of response to therapy was done at the beginning of study, in the six and in the 12- month follow-up to evaluate size, thickness, texture and subjective symptomatology (e.g. burning, pruritus), on the basis symptom improvement, photographic record and observations of an independent observer. We have a final assessment after one year for each patient in three categorical groups: patients with recurrent keloids; patients with partially keloid recurrence; patients with keloid free. The final analysis was based on comparison of one year flow up outcomes in patients of two groups. The data collected were analyzed by SPSS statistical software with using tables and  $\chi$  square tests.

## Results

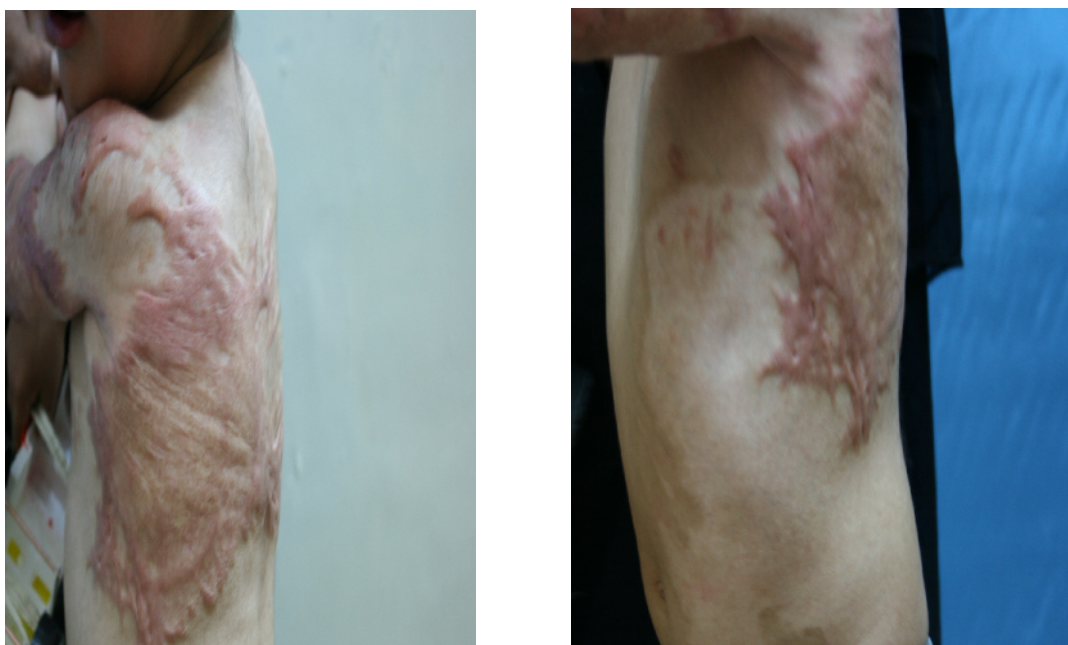
The aim of this study was survey of adjuvant treatment of intralesional 5-fu effectiveness in prevention of keloid recurrence. We compared two groups of patients treated with and without 5-FU.

Our study showed keloids were completely cured in 18 (75%) of cases and there was an improvement in size and consistence in 5 (21%) of cases with total satisfactory response in 23 (96%) of cases versus 10 (43%), 8(35%) and 18 (78%) in control group patients, respectively (Table 1).

The side effects commonly encountered, were pain at the injection site, ulceration and burning sensation not significantly different in tow groups (Figure 1, 2).



Figure 1. 25 year old women , keloid former followed by flame burn. PreOp (left) and 6months postOp (right) (trial group)



**Figure 2.** 18 year old men, keloid former followed by flame burn. PreOp (left) and 10 months postOp (right) (control group)

**Table 1.** Compare of treatment outcomes in patients of trial group and patients of control group

Group study	Keloid recurrence	Keloid partially improvement	Keloid free	Total
Cases	1 (4%)	5 (21%)	18 (75%)	24 (100%)
Controls	5 (22%)	8 (35%)	10 (43%)	23 (100%)
Total	6 (13%)	13 (30%)	28 (57%)	47 (100%)

$$\chi^2 = 5.63, df = 2, P < 0.05$$

## Discussion

Keloids are abnormal fibrous growths that result from a connective tissue response to trauma, inflammation, surgery, or burns or they occasionally occur spontaneously. These fibrous growths cause significant cosmetic and symptomatic problems in the form of pruritus, pain and restriction of movement by lesions close to the joints (10). Although optimal treatment of keloids remains undefined, good results can be obtained through a multimodality approach (11). The response of these lesions to treatment are very difficult in spite of the wide range of therapeutic options, including retinoid, irradiation, intralesional corticosteroids, cryosurgery, silicone gel, pressure, surgery, and newer modalities such as pulsed dye laser, interferon  $\alpha 2b$  and cultured epithelial autograft. The reported efficacy of each of these is variable, and each has its own attendant side effects (3). The combined use of surgery and intralesional corticosteroid infiltration is still today a successful treatment and provides the best means of support (2, 3, 5) together with this therapy, applied

pressure and topical silicone sheets have been useful. However, these can lead to atrophy, telangiectasia, necrosis, ulceration, hypopigmentation, and Cushingoid shape. Also, recurrence is a problem (3).

5-FU a pyrimidine analogue chiefly used as a chemotherapeutic agent because of its antimetabolite activity, has been found to inhibit wound healing and have an inhibitory effect on human fibroblast cell lines in culture. It also inhibits proliferation and myofibroblast differentiation in dupuytren fibroblasts in vitro (12). In agreement with the literature, we have seen good results in majority of the patients as has been previously reported (4, 5). Also, keloids of long duration up to 15 years as well as large size were seen to respond to combination of topical silicone and 5-FU. In our series, treatment of keloids by perilesional surgical excision, topical silicone, intralesional injection of 5-FU at timed intervals, offered a higher rate of resolution than other therapeutic strategies and some other series (13, 14), without any significant difference in recurrence rates related to sex and age, while in the sternum location there was a higher percentage of recurrence

(Table 1), (Figures 1&2). We concluded 5-FU combined with topical silicone is an effective and safe treatment for keloids of all sizes and any duration. We noted more than 60% improvement in majority of cases but few of them showed 100% clearance.

Eighteen patients (75%) keloid free in cases versus ten patients (43%) in controls that is significant ( $P=0.025$ ) table 3. Results show that therapy with surgery, topical silicone, combined with adjuvant treatment of intralesional 5-FU, has success rate more than 30% in keloid recurrence prevention.

The modality of combined 5-FU and topical silicone is a sound approach for prevention of keloids.

### Study limitation

The sample size was fifty keloid patients that was not enough, this should be confirmed by other randomized clinical with greater sample size.

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### Conflict of interests

The authors declare that they have no competing interest.

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