

Role of 5-Fluorouracil (5-Fu) in Remodelling of Eyelid Scars: Our Experience

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Abstract

Eyelid scars usually aren't thick, but they're important because they inhibit the movement of small, delicate structures. For concerns, both cosmetic and functional, post-traumatic scarring of eyelids and periorbital area can pose a challenge for ophthalmologists. But the antimetabolite 5-fluorouracil (5-FU) offers a versatile option for approaching this common problem. 5-FU injections given at the first sign of contracture can help minimize scar tissue and dramatically improve eyelid function. Given its proven and long-standing track record in oncology, off-label applications of 5-FU have expanded in recent years into orbital and adnexal efforts to modify keloids and hypertrophic scars.

Keywords: 5FU, fluorouracil, hypertrophic scars, cicatricial ectropion.

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INTRODUCTION

Periorbital and eyelid scars usually result due to mechanical trauma, chemical injury or burns. Such scars on conspicuous areas of face can be aesthetically disfiguring and can even result in functional loss of eyelids. Correcting disfigurement and cicatricial ectropion in such patients pose challenge for oculoplastic surgeons. With the advancement in the field of medicine and oculoplasty, various drugs have evolved which have been used as adjuvants with surgery in such conditions like corticosteroids, mitomycin-C, 5-fluorouracil, tamoxifen citrate, methotrexate, interferons, imidazoquinolines, retinoids, etc [1]. 5-Fluorouracil is an anti-metabolite which is being used as an anti-cancer drug in the treatment of carcinoma colon, esophagus, pancreas, stomach, breast and cervical cancer [2]. Studies have reported its off-label use as intralesional injections for the treatment of keloids and hypertrophic scars [3] and after application of full-thickness skin grafts for better uptake of graft [4]. To the best of our knowledge, there has been very scarce evidence in literature on 5-FU being used for post traumatic scars. This study was carried out to evaluate the effect of subcutaneous injection of 5-FU on periorbital and eyelid scars.

MATERIAL AND METHODS

The study was conducted in a tertiary eye care hospital in North India from May 2016 to October

2018. 15 patients with periorbital and lid scars by any kind of trauma presenting to our oculoplastic clinic were enrolled in the study. Informed consents were taken which included advising the patient regarding the off-label use of the medication. Potential risks associated with the medication such as pain, urticaria, skin changes, skin breakdown, pigment changes, and possible systemic absorption were discussed with the patients. Patients were also counselled regarding other treatment options.

Exclusion criteria followed was:

- Pregnant and lactating women
 - Patients with active infections
 - Patients with chronic illnesses like renal failure, hepatic failure, acid peptic disease, diabetes, and hypertension
 - Immunocompromised patients
- All such patients were excluded from the study.

At first visit, detailed history of patients were recorded in the proforma including name, age, sex, address, presenting complaints, duration of complaints, nature of injury, mode of trauma, systemic history and family history. Complete general and ocular examination was done including visual assessment, oculoplastic work-up, slit lamp examination, and fundus examination to look for any other signs of

trauma. Digital photographs of every patient were taken.

All the patients were given 0.4 – 0.6 ml of 5-flourouracil (50mg/ml) injection subcutaneously, under all aseptic precautions, at the site of scar, for atleast 3 injections every 4 weeks, and maximum of upto 6 injections. At each visit, patients were evaluated for redness, swelling, tissue inflammation/atrophy, telangiectasis, and pigmentary disturbances. At subsequent visits, digital photographs were taken for the records. Patient interpretation of outcome was determined subjectively by asking if they were satisfied and objectively by comparing their initial and subsequent digital photographs.

RESULTS

The study comprised of a total of 15 patients among whom 9 (60%) were males and 6 (40%) were female patients (Table 1). The mean age of the group was 31.33 years ranging from 17 years to 60 years. In 9 (60%) patients, right eye was involved while in 6 (40%) patients, left eye was involved. As far as site of scar is concerned, in 8 (53.33%) patients, lower lid was involved, in 2 (13.33%) patients, upper lid was

involved, in 4(26.66%) patients, both upper and lower lids were involved, while in 1(6.6%) patient, only lateral canthus was involved. Mean duration between the time of injury and application of first dose of injection was 19.2 weeks ranging from 3 weeks to 2 years. The average number of injections given to patients was 5.5. 11 (73.33%) patients received a total of 6 injections and 4 (26.66%) patients received 4 injections. All the patients (100%) were satisfied with the treatment. Symptomatic improvement was described by patient as scarred skin being ‘less tight’ and improvement in facial appearance. Objective improvement was determined by comparing their initial and subsequent digital photographs which was seen in 100% patients (Figure 1). One patient out of 15 (6.6%) developed telangectasia of overlying skin after receiving 4 injections (Figure 2). Further injections were withheld in that patient. 4 patients had to undergo surgery for correction of their cicatricial ectropion even after receiving 6 injections. Full thickness skin grafting was done in 3 patients out of 4, and lateral tarsal strip procedure was done in one patient (Figure-3). These patients were given 3 more injections of 5-FU at 2 weekly interval post-op which resulted in better uptake of graft and less scarring.

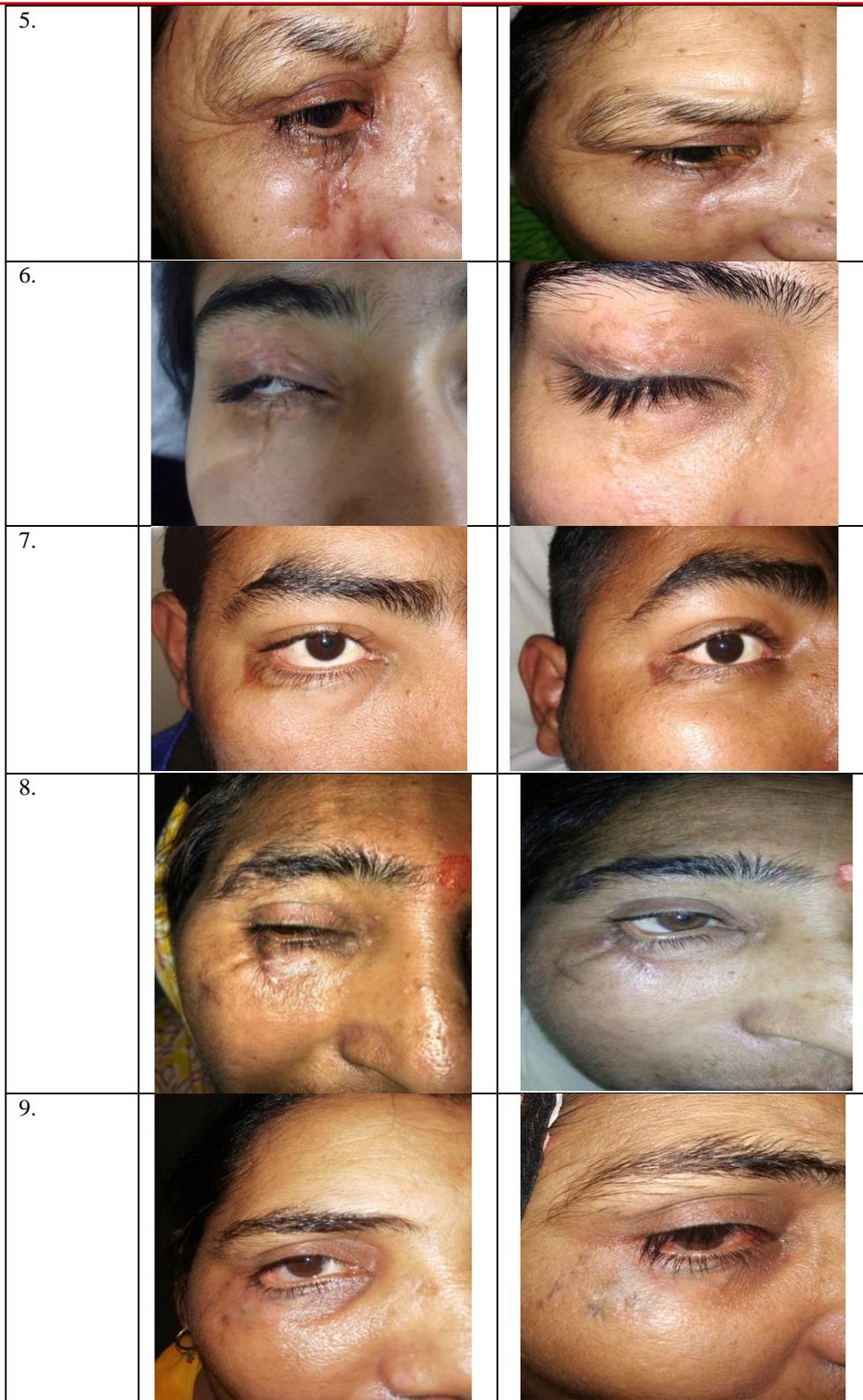
Table-1: Table showing demographic and clinical profile of patients

Patient No.	Age (yrs)	Sex	Eye	Eyelid	Duration between Injury and First Injection	No. of Injections	Improvement	Side Effect	Final Correction
1	25	M	Left	LL	4 weeks	4	Yes	No	
2	19	M	Right	UL	20 weeks	6	Yes	No	
3	21	M	Left	LL	30 weeks	6	Yes	No	Surgery (full thickness skin grafting)
4	38	F	Left	UL,LL	30 weeks	6	Yes	No	
5	60	F	Left	UL,LL	3 weeks	6	Yes	No	
6	20	F	Right	UL,LL	5 weeks	6	Yes	No	
7	22	M	Right	LL	6 weeks	4	Yes	No	
8	43	F	Right	LL	52 weeks	6	Yes	No	Surgery (full thickness skin grafting)
9	45	F	Right	LL	6 weeks	6	Yes	Yes, Telangectasia of skin	
10	17	M	Right	LL	4 weeks	4	Yes	No	
11	46	M	Right	UL,LL	5 weeks	6	Yes	No	

12	35	M	Left	UL	104 weeks	6	Yes	No	Surgery (full thickness skin grafting)
13	40	F	Right	LL	4 weeks	6	Yes	No	
14	18	M	Right	LL	6 weeks	6	Yes	No	Surgery (lateral tarsal strip procedure)
15	21	M	Left	Lateral Canthus	8 weeks	4	Yes	No	

M= Male, F= Female, UL= Upper lid, LL= Lower lid

Patient No	Before Injections	After Injections
1.		
2.		
3.		
4.		



10.		
11.		
12.		
13.		
14.		



Fig-1: Comparison of digital photographs of patients taken before and after 5-FU injections



Fig-2: Photograph of a patient showing telangiectasia of skin after 5-FU injections

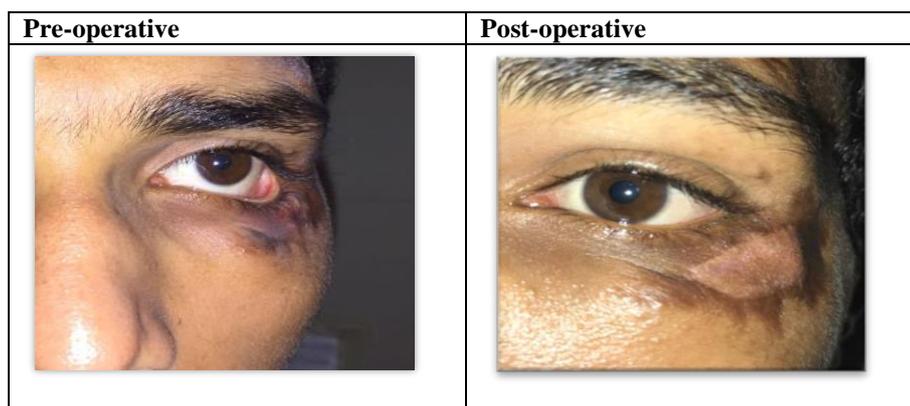




Fig-3: Clinical photographs of 4 patients who underwent surgical correction for cicatricial ectropion

DISCUSSION

Scarring is a physiological process of healing of the wound. Fibroblasts are vital constituents of the normal wound-healing processes [5]. There are three distinct stages of wound healing: inflammation, proliferation, and maturation. First, leukocytes and macrophages clean the wound of cellular debris and bacteria to prevent infection. Next, fibroblasts produce collagen, which gives tissue its tensile strength and structure. The wound site fills with granulation tissue, and the margins contract with the mobility of myofibroblasts allowing for epithelization. Finally, collagen fibers remodel to improve the overall tensile strength [5].

5-Fluorouracil is a pyrimidine analogue that inhibits the synthesis of deoxyribonucleic acids (DNA) by irreversibly inhibiting thymidine synthase, which is

responsible for converting uridine to thymidine [2]. So, 5FU only works on cells that are metabolically active and proliferating, instead of causing collateral damage to surrounding cells. It halts rapidly proliferating cells such as fibroblasts and hence scar degradation is promoted. Additionally, 5-FU is believed to hinder type I collagen gene expression and the effects of tumor growth-beta 1 [3]. 5-FU, an antimetabolite, first came into medical use in 1962 and is being used as an anti-cancer drug for the treatment of carcinoma colon, esophagus, pancreas, stomach, breast and cervical cancer.[2] In ophthalmology, it is being used as an off- label drug. 5-FU was used as early as the 1980s to improve the results of trabeculectomy [6] and now-a-days it is used as a primary treatment of ocular surface squamous neoplasia (OSSN) [7]. It has also been injected intralesionally for the treatment of nodular basal cell carcinoma and keratoacanthoma [8-10].

In 1999, Fitzpatrick introduced 5-FU for the treatment of hypertrophic scars and keloids for the first time [3]. Gupta *et al.*, also suggested 5-FU is effective in treatment of keloid scars [11]. These studies have discovered a dose-related association between 5-FU and reduction in keloid fibroblast proliferation and the fibroblast-populated collagen lattice. Haurani *et al.*, reported a 50% median decrease in scar volume in the hypertrophic scars and decreased recurrence rate of keloids after treating with 5-FU [12]. Massry *et al.*, described their experience with postoperative intralesional injection of 5-FU with or without added low-dose concentration steroid, in the 19 patients undergoing eyelid skin grafting surgery. The author concluded that the 5-FU is effective with "minimal scarring, high patient (89%) and surgeon satisfaction (95%), and few complications [4].

In our study, the patient satisfaction was 100%, although we evaluated the response in traumatic scars only and not specifically in skin grafting cases. However, in our three cases that underwent skin grafting for cicatricial ectropion, the graft uptake was good without any complications even after 6 months of follow-up. Many studies have compared the effectiveness of combination of 5-FU and triamcinolone with either 5-FU or triamcinolone administered alone and have found the combination to be more effective but the demerits of steroids are its unpleasant side effects including telangiectasia, fat atrophy, rebound effects, ineffectiveness, and the painful drug deposits [13-17]. On the other hand, side effects of 5-FU are usually seen with intravenous dosing and primarily involves adverse hematologic effects such as anemia, thrombocytopenia, and leukopenia [2]. None of the previous studies on intralesional 5-FU have reported any systemic side effects, rather few patients have reported erythema, ulceration, depigmentation or significant pain at the injection site. These were generally transient or easily manageable [18]. In our study, one patient reported telangiectasias over injection site. Overall the results were very gratifying but further large scale, long-term studies with more objective outcome parameters are needed to discuss the effectiveness and complications of 5-FU in periorbital and eyelid scars.

CONCLUSION

While surgical advances in minimally invasive surgical techniques continue to evolve, there is a definite and necessary role for nonsurgical adjunctive methods, which address the underlying biologic process of wound healing and scar formation. These include the utilization of antimetabolites and anti-inflammatory agents (5-FU, corticosteroids) and injectable tissue fillers with tissue volume expansion. Subcutaneous injections of 5-FU is an effective therapy in reducing post-traumatic periorbital and eyelid scars. . In the future, we await the production of other modulators that

can target the mechanisms for scar formation more specifically

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