

Comparative Study between Intralesional Injection of Triamcinolone Alone and Combination of Triamcinolone and 5-Fluorouracil in Treatment of Hypertrophic Scars and Keloids

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ABSTRACT

Background: Hypertrophic scars and keloids represent an entirely highly challenging frustrating clinical and cosmetic problem. Various modalities and protocols were suggested. Intralesional injection of Triamcinolone (TAC) has proved marked improvement in scars and keloids. On the other hand, combination of Triamcinolone and 5-Fluorouracil (5-FU) as well proved its efficacy over the past fifteen years in treatment of hypertrophic scars and keloids.

Material and Methods: Twenty lesions were presented in this study. All lesions were subjected to intralesional injection of triamcinolone alone in half of the surface area of the lesion and combination of triamcinolone and 5-Fluorouracil in the other half of the lesion. All patients were followed-up till six months after the last session. They were assessed by the researchers helped by digital photographs according to five evaluation criteria together with patient satisfaction.

Results: In comparing intralesional injection of Triamcinolone alone and combined with 5-Fluorouracil we found both modalities were effective with superiority of triamcinolone over combination especially in hardness and elevation of the lesions.

The patients treated with combined Triamcinolone and 5-Fluorouracil experienced side effects such as hyperpigmentation, pain at the injection site, and superficial ulceration. These side effects were less in patients treated with Triamcinolone alone.

Conclusion: It appears from this study that Triamcinolone is a better tolerated and less toxic alternative to combined Triamcinolone and 5-Fluorouracil in the management of keloids and hypertrophic scars, and treating such benign disease with an anticancer drug like 5-Fluorouracil does not give any special advantage over Triamcinolone.

Key Words: *Hypertrophic scars – Keloids – Triamcinolone – 5-Fluorouracil.*

INTRODUCTION

Hypertrophic scars and Keloids are benign disfiguring cutaneous lesions that are produced by uncontrolled synthesis and deposition of dermal collagen during and after wound healing process in predisposed individuals. Patients with keloids or hypertrophic scars suffer a severe impairment

of quality of life, by causing physical, psychological and social squeals, although it is a common lesion following wounds and the prevalence of hypertrophic scarring following burns is about 67%, but further epidemiological research is still necessary. Excessive scarring represents the first morbidity cause in burn survivors [1].

Hypertrophic scars and keloids are abnormal wound responses in predisposed individuals and represent a connective tissue response to trauma, inflammation, surgery, or burns. The first challenge to scar therapy begins with the simple identification and diagnosis of the problematic abnormal wound healing. Hypertrophic scars are typically raised, red or pink, and sometimes pruritic but do not exceed the margins of the original wound, whereas keloids infiltrate into surrounding normal tissue and rarely regress, hypertrophic scars usually subside with time, whereas keloids continue to evolve over time, without a quiescent or regressive phase [2].

A wide range of therapies exist for hypertrophic scars and keloids. But despite the multiple treatment modalities available, they still remain a significant challenge for both the clinician and the patient and the definitive treatment for hypertrophic scars and keloid not well settled yet.

Intralesional corticosteroid injections improve scar pliability, diminish its volume and height and reduce scar-related itching and pain. The most used current protocol involves insoluble Triamcinolone acetate (TAC) (10-40mg/ml), alone or better in combination with lidocaine, weekly, biweekly or monthly. It has been reported that corticosteroids suppress healing and pathological scarring by three mechanisms: Anti-inflammatory and immunosuppressive effect, vasoconstriction, and inhibition of fibroblast and keratinocyte proliferation due to an antimitotic effect [3].

Fluorouracil (5-FU) is a chemotherapy drug, a pyrimidine analog with antimetabolite activity, effective in the treatment of keloid scars, especially during the first 5 years of appearance. Wound ulceration, hyperpigmentation and pain are potential complications of the treatment. Weekly intralesional 5-FU injections (50mg/ml) for 12 weeks resulted in reduction in scar size of at least 50% with no recurrence in 24 months. The double combination of 5-FU, corticosteroids is a successful multifaceted approach for the treatment of hypertrophic scars and keloids [4].

MATERIAL AND METHODS

After approval of Research Ethical Committee of Faculty of Medicine, Fayoum University, this prospective study was performed at plastic surgery outpatient clinic, Fayoum University Hospital on 20 lesions of hypertrophic scars and keloids in the period from March 2014 to March 2015.

All patients or the parents or guardians of cases signed an informed consent about the procedure and material used and its possible side effects and the course of the treatment, lesions were photographed before and after the sessions.

The patients were divided into 2 groups:

Group A: Included 10 lesions (5 females and 5 males) with hypertrophic scar within each patient.

Group B: Included 10 lesions (1 female and 9 male) with keloid within each patient.

The lesion was divided equally by a line according to the meridian of the lesion into two sides called T and F.

T: The side of the lesion which will be injected with triamcinolone (Triamcinolone acetonide (40mg/ml) can be diluted with 2% xylocain in a ratio up to 1:2).

F: The side of the lesion which will be injected with combination of 5-Fluorouracil and triamcinolone. ([TAC + (5-FU)], 0.1mL of 40mg/mL TAC was added to 0.9mL of 5-FU (50mg/mL). The ratio TA-5 FU will be 1-9).

Intralesional injection was performed in all the lesions. The procedure was done at the outpatient clinic of Plastic Surgery at Fayoum University Hospital.

Each lesion in both groups was marked transversely at the centre of its longitudinal axis and divided into two zones the zone towards right or upper half will be injected by triamcinolone alone while the zone towards the left or lower half will

be injected by combination of triamcinolone and 5-Fu.

The recommended concentration of 5-FU (50 mg/1ml) does not exceeding 100mg i.e., up to 2ml in each lesion per session.

Triamcinolone acetonide (40mg/ml) can be diluted with 2% xylocain in a ratio up to 1:2 as combination to infiltrate the lesion not exceeding 40mg per session i.e. 3ml of diluted triamcinolone.

Intralesional triamcinolone acetonide (TAC, 40mg/mL) was injected according to the dose described above at weekly intervals for a total of 4 weeks, then monthly for 4 months. Other side of the lesion [TAC + 5-fluorouracil (5-FU)], 0.1mL of 40mg/mL TAC was added to 0.9mL of 5-FU (50mg/mL). The ratio TA-5 FU will be 1-9, this combination was injected weekly for 4 weeks then monthly for 4 months the same as the other half of the lesion.

During the course of injection which is 5 months. Results were compared by photographs all through, together with researcher's direct clinical evaluation.

Final assessment was done according to scoring system (Table 1) within 3 days after the last session and after six months from the end of the course of injection; assessment was done by investigator's direct clinical evaluation aided by photos of each patient.

Table (1): Scoring criteria [5].

Criteria	Score
A- Redness	3: Severe redness associated with telangiectasia. 2: Redness disappears with pressure. 1: No redness but a dark appearance. 0: Normal skin color.
B- Elevation	3: More than 6mm in height above the surrounded skin. 2: 3-6mm. 1: 1-3mm. 0: Flat or depressed scar.
C- Hardness	3: Very hard, like a cartilage. 2: Rubbery hard. 1: Partially soft. 0: Soft.
D- Itching	3: Severe itching sensation, or constantly itchy with signs of scratching. 2: Occasional itchy sensation, moderate and tolerable. 1: Sometimes itchy. 0: No itchy sensation.
E- Tenderness and pain	3: Severe irritable pain. 2: Moderately irritable pain. 1: Sometimes painful. 0: Without pain.

The lesions were evaluated clinically according to the score system in 5 criteria: Redness, elevation, hardness, itching, tenderness and pain with scoring from 0-3.

The evaluation of response was graded as follows:

I- Minimal response. 0-25%.

II- Moderate response: 25-50%.

A- Change of one score in no more than 3 criteria.

B- Change of one score in no more than 2 criteria provided that one or more criterion was ranking 0 score before embarking upon our treatment.

III- Marked response: 50-75% improvement more than minimal and less than complete.

IV- Excellent response: 75-100% change of the score into 0 in all criteria.

Statistical analysis of data:

The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 19 (SPSS Inc, USA). For quantitative data, the mean and standard deviation were calculated. Independent *t*-test was used to compare between two types of lesion regarding different variables of the study. Paired *t*-test was used in comparing between the difference of parameters before and after injection. For qualitative data the number and percent distribution was calculated, chi square (χ^2) was used as a test of significance. For interpretation of results of tests of significance, significance was adopted at $p < 0.05$ and high significant was taken on at $p < 0.001$.

RESULTS

During the study period (from March 2014 to March 2015) 20 lesions of hypertrophic scars and keloids were enrolled in this study. 14 males (70%) and 6 females (30%). Age ranged from 3 to 53 years with (mean age 26 years). 35% caused by cut wound (7 lesions), 50% caused by burn (10 lesions) 5% post abscess drainage (1 lesion), 5% sternotomy incision (1 lesion), 5% caused by skin grafting (1 lesion).

There was no significant difference between two types of lesion for age or sex.

Comparing variables in Group A (Hypertrophic scars) Fig. (1):

A comparison between the T side and the F side of the lesion, results were compared by photographs all through, together with patient satisfac-

tion, researcher's direct clinical evaluation as regards scar improvement, in the five criteria elevation, itching, pain, redness, and induration.

Regarding pain, the mean of pain score was significantly decreased after last injection in both groups (TAC vs Combined TAC & 5-FU), p -value < 0.0001 (Highly Significant) (HS). But the decrease in pain was more characteristic in TAC alone (75.0%) than combined TAC & 5-FU (62.5%). There was no change after six months follow-up $p = 1.000$ (None Significant) (NS).

While in itching the improvement in both groups was statistically significant (p -value < 0.0001 (HS), but the superiority in improvement was in TAC alone (71.4%) more than Combined TAC and 5-FU (66.6%).

Regarding hardness, there was significant improvement after last injection in both groups (TAC vs combined TAC & 5-FU), p -value < 0.0001 (HS). But the improvement was more characteristic in TAC alone (75.0%) than Combined TAC & 5-FU (45.8%), there was no change after six months follow-up, $p = 1.000$ (NS).

The major disparity between the two groups was in elevation, improvement was noticeable and statistically significant (p -value < 0.0001 (HS), in combined TAC & 5-FU (52.4%) but more characteristic in TAC (85.7%) and there was further improvement (10.0%) in combined TAC & 5-FU injection after six months (accumulative effect) while change in TAC alone was insignificant ($p = 0.343$ (NS).

In redness the improvement in both groups was statistically significant (p -value < 0.0001 (HS) but the superiority in improvement was in TAC (68.2%) with no recurrence after six months while in combined TAC & 5-FU the improvement was (40.9%) with deterioration after six months follow-up (15.4%) $p = 0.157$ (NS).

Comparing variables in Group B (keloids) Figs. (2,3):

A comparison between the T side and the F side of the lesion, results were compared by photographs all through, together with patient satisfaction, researcher's direct clinical evaluation as regards scar improvement, in the five criteria; elevation, itching, pain, redness, and induration.

Regarding pain, the mean of pain score was significantly decreased after last injection in both groups (TAC vs. combined TAC & 5-FU), and (p -value < 0.0001 (HS) but the decrease in pain was more characteristic in TAC alone (69.6%) than

combined TAC & 5-FU (60.9%). There was no change after six months follow-up $p=1.000$ (NS).

While in itching the improvement in both groups was statistically significant (p -value <0.0001 (HS), but the improvement was almost the same in TAC alone (60.7%) and combined TAC & 5-FU (60.7%). After six months follow-up there was recurrence of itching in combined TAC & 5-FU (45.5%), which is significant, $p=0.015$ (S).

Regarding hardness, there was significant improvement after last injection in both groups (TAC vs. combined TAC & 5-FU), p -value <0.0001 (HS). But the improvement was more characteristic in TAC alone (66.6%) than Combined TAC & 5-FU (40.0%), there was no change after six months follow-up, $p=1.000$ (NS).

The major disparity between the two groups was in elevation, improvement was noticeable and statistically significant (p -value <0.0001 (HS), in

combined TAC & 5-FU (37.5%) but more characteristic in TAC alone (70.8%), after six months follow-up there was no significant change $p=1.000$ (NS).

In redness the improvement in both groups was statistically significant (p -value <0.0001 (HS) but the superiority in improvement was in TAC alone (75.9%) with no recurrence after six months while in combined TAC & 5-FU the improvement was (31.0%) with recurrence in 20.0% of cases, $p=0.037$ (S) after six months follow-up.

Side effects and sequelae reported:

Follow-up was done at least six months after the last injection session for local complications (allergy, transient erythema, infection, oozing, superficial ulceration, hyperpigmentation in combination of 5-Fu injection or hypopigmentation in TAC injection, and pain) fat atrophy (with triamcinolone injection) (Table 2).

Table (2): Local complications of intralesional injection.

Complication	Number of patients	Site (TAC or combined 5-FU+TAC)	Onset	Special notes
Superficial ulceration	12 (60% of cases)	Combined 5-Fu + TAC	After 2-3 sessions	• Healed spontaneously • Topical panthanol and fusidic acid was beneficial
Erythema	20 (100% of cases)	Both	All sessions after injection	• Temporary, regress spontaneously
Hyperpigmentation	18 (90% of cases)	Combined 5-Fu + TAC	After 2 sessions	• Increase with every injection
Infection	2 (10% of cases)	TAC	After 5 sessions	• Abscess formation
Hypopigmentation	1 (5% of cases)	TAC	Around scar (in normal skin)	—
Allergy	0	—	—	• Occur Immediately or shortly after injection
Fat atrophy	1 (5% of cases)	TAC	—	• Caused by bad injection technique



Fig. (1): (A,B): Hypertrophic scar on back of left forearm before injection, (A) Top view, (B) Tangential view, (C): Same patient after six months of last injection, TAC was injected in the upper side of lesion and combination was injected in the lower side.

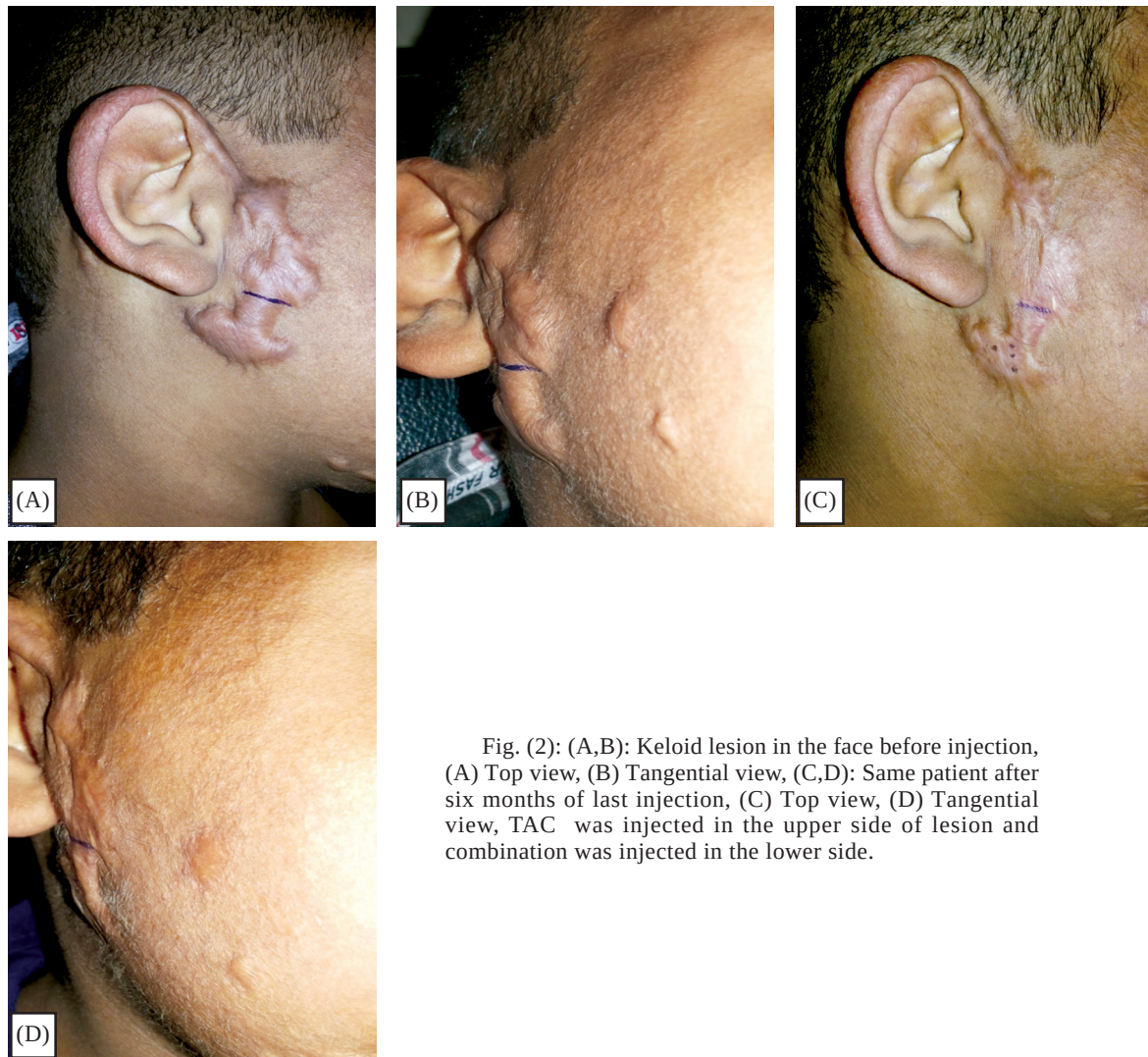


Fig. (2): (A,B): Keloid lesion in the face before injection, (A) Top view, (B) Tangential view, (C,D): Same patient after six months of last injection, (C) Top view, (D) Tangential view, TAC was injected in the upper side of lesion and combination was injected in the lower side.

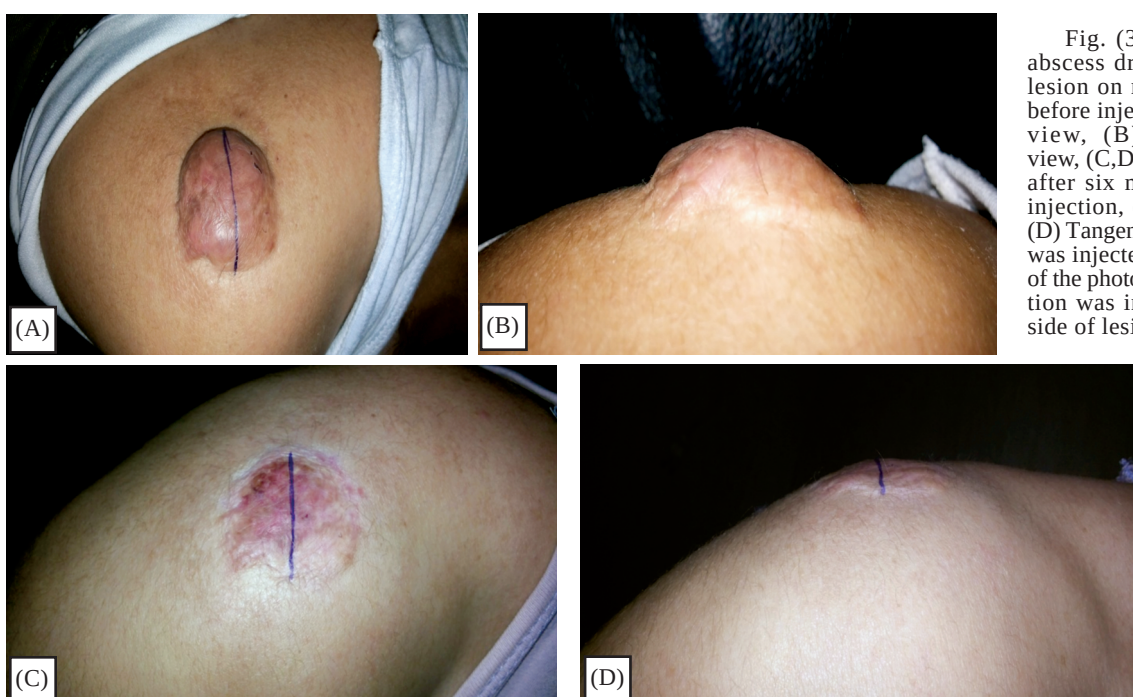


Fig. (3): (A,B) Post abscess drainage keloid lesion on right shoulder before injection, (A) Top view, (B) Tangential view, (C,D) Same patient after six months of last injection, (C) Top view, (D) Tangential view, TAC was injected in right side of the photo and combination was injected in left side of lesion.

DISCUSSION

Although many articles have been published on the management of keloid and hypertrophic scars, there is no universally accepted treatment protocol. And still there is debate in treatment decision in scar management.

Hypertrophic scars may be more responsive to treatment than keloids, which are often resistant to treatment and have a higher rate of recurrence [6].

Laser, surgical removal, radiotherapy, silicone gel sheeting and other dressings, cryotherapy, interferon, bleomycin, 5 fluorouracil, and intralesional corticosteroids have all been used alone or in various combinations, with variable but largely transient success [7].

There are various combination therapies that have been used to treat keloids and hypertrophic scars. Intralesional steroid injections have been combined with adjuvant therapies, such as surgical excision to beneficial effect.

Intralesional injection of triamcinolone and 5-fu or combination of both is well known and most effective treatment for hypertrophic scars and keloids, but there still deficiency in studies that evaluate their effect specially on Egyptian patients.

We have made comparative study so as to evaluate its effect, benefits and side effect on keloid and hypertrophic scar affected patients.

The efficacy of intralesional corticosteroid injections in the treatment of keloids and hypertrophic scars has been well established, and they have been a mainstay in the treatment of keloids and hypertrophic scars, alone or in combination with other modalities.

A clinical review (LOE-4) showed that 18 patients with dark pigmented skin treated with core excision and delayed intralesional steroid injection were successfully treated without recurrence [8].

Corticosteroids reduce excessive scarring by decreasing collagen synthesis, glycosaminoglycans synthesis, the expression of inflammatory mediators, and fibroblast proliferation during wound healing. A well documented corticosteroid in the intralesional application is Triamcinolone Acetonide (TAC) [9].

Recent evidence suggests that 5-FU selectively blocks collagen synthesis, which may augment its

antiscar role. Intralesional 5-FU administration is safe, provided the recommended upper limit of the dose is not breached; the toxicity is related to intravenous dosage, not subcutaneous [10].

Side effects like erythema and ulceration are common when pure 5-FU is used. Small concentration of TAC is added in order to reduce these local side effects. This small amount of TAC has no role in efficacy.

Fitzpatrick published his 9-year familiarity with the use of TAC + 5-FU. He had the experience of over 5000 injections to more than 1000 patients. He reported that addition of TAC to 5-FU produced more effective results and reduced the pain. Combination was made by addition of 0.1mL of 40 mg/mL TAC to 0.9mL of 50mg/mL 5-FU. Injections were repeated for a mean of 5 to 10 times. Dosage of drug and duration of exposure had been found as major determinants of fibroblast degeneration [11].

Gerd G. Gauglitz recommended and used a method for intralesional TAC 10mg (0.25ml of 40mg/ml TAC diluted with 0.75ml injectable normal saline) was administered once weekly for a total of 8 sessions [12].

It has been reported that 5-FU delivered intralesionally once weekly or once every 2 weeks to keloids and hypertrophic scars is effective [9].

It was observed by a study that using combination of TAC + 5FU resulted in more than 50% improvement in about 80% patients. In comparison with TAC group, it looks as if TAC + 5-FU combination is more effective [1].

Another study was carried out on 40 patients found that both groups showed acceptable improvement in nearly all parameters but more in combination group than Triamcinolone (TAC) alone except pruritus and itching reduction were better improved with TAC [13].

Konchristopoulos observed 85% of patients with more than 50% improvement, but significant recurrence was seen in 45% and ulceration in 30% cases in 12-month follow-up [14].

One study compared 5-FU + TAC with TAC alone. It observed good to excellent (>50%) improvement in 20% of the patients in TAC alone group, and 55% of the patients in the combination group, and on the observer assessment scale good to excellent response was reported in 15% in TAC alone, and 40% in the combination therapy [15].

In the current study, 45mg of 5-FU (0.9ml of 250mg/5ml) was mixed with 4mg TAC (0.1ml of 40mg/1ml). This combination is documented as more effective and gives rapid response with fewer side effects [10]. We used (Triamcinolone acetonide (40mg/ml) which can be diluted with 2% xylocain in a ratio up to 1:2) injected to one half of the lesion (T side) and [TAC + (5-FU)], 0.1mL of 40mg/mL TAC was added to 0.9mL of 5-FU (50mg/mL). The ratio TA-5 FU will be 1-9 for the other half of the lesion (F side).

Our injection protochole was weekly for 4 weeks then monthly for 4 months for a total period of treatment of 5 months, then follow-up of the patient for six months for recurrence of symptoms.

In the current study no serious systemic side effects were observed among TAC + 5-FU group. Based on pharmacokinetic studies, 5-FU remains in the soft tissue for less than 10 days. Once taken up in the bloodstream, it is degraded within 20 minutes. The metabolites are excreted by the kidney.

Drug toxicity is related to intravenous dosing; not subcutaneous. Systemic 5-FU can cause anemia, leukopenia, and thrombocytopenia.

Although dose of 5-FU was not more than 90mg at each injection session, the administration of higher doses has been described without development of any undesirable haematologic effects [16].

In this study, we found that both modalities of treatment were similarly 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, hyperpigmentation in 90% of cases, ulceration and tissue sloughing were seen in 60% of our patients, which took a few weeks to heal. This has been observed in other studies also [1,4,14].

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 not noted during the follow-up duration of six months. Konchistopoulos et al., reported 47% recurrence in the improved patients treated with 5-FU [14].

Conclusion:

In this study comparing the efficacy of intralesional injection of Triamcinolone alone and combined with 5-Fluorouracil we found both effective

and acceptable for treatment of keloids and hypertrophic scars the overall efficacy of both modalities were comparable and close together with superiority of Triamcinolone especially in hardness and elevation of the lesion.

Considering the above facts, it appears that treatment for a benign disease like keloids and hypertrophic scars with an anticancer drug like 5-FU does not give any special advantage over Triamcinolone acetonide. The patients treated with combined TAC+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 combined TAC + 5-FU in the management of keloids.

We think it will be a little diffusion of one product into the other' territory but it will be mainly at the junction area and we evaluated the whole territory and we decided to do the comparison at the same lesion to get more accurate data.

It is becoming more and more important to recognize these differences and treat keloids as a separate entity different from hypertrophic scars. Understanding the genetic basis of keloid disease and hypertrophic scars may provide future prognostic and diagnostic advice to patients. This will likely lead to more specific and effective treatments in the future.

Conflicts of interest:

The authors declare that there are no conflicts of interest or financial affiliations specific to this study.

Ethical approval:

Was obtained.

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