Original Research Article

Comparative Study between the Efficacy of Interalesional Triple Therapy by (5-Fluorouracil, Triamcinolone and Hyaluronidase) Versus Interalesional Drug Monotherapy in the Treatment of Keloid

Abstract

Background: Keloid is a type of scar with formation of either type III (early) or type I (late) collagen. This study aimed to evaluate the clinically and microscopely efficacy of intralesional triple therapy by 5-fluorouracil, triamcinolone acetonide and hyaluronidase versus intralesional injection of 5-fluorouracil and triamcinolone and Hyaluronidase each alone in treatment of Keloids.

Methods: This prospective study included forty patients diagnosed clinically and histologically with Keloid. Patients were divided into 4 equal groups: group I (given triple intralesional injection therapy of total 1 ml solution of the combination of 5- fluorouracil and Triamcinolone), group II (given intralesional injection of 5-fluorouracil and each 1 cm^2 of keloid was injected by 0.3 ml of the solution), group III (given intralesional injection of triamcinolone and each 1 cm^2 of keloid was injected by 0.3 ml of the solution) and group IV (given intralesional injection of hyaluronidase and each 1 cm^2 of keloid was injected by 0.3 ml of the solution). Patients were subjected to full history taking, clinical examination [general and dermatological], digital photography of the lesions and tissue punch biopsies.

Results: Blind dermatologist and patient satisfaction was significantly higher in group I compared to other three groups ($P<0.05$) , was significantly lower in group II compared to

group III and IV group (P=0.003, P=0.004, P=0.034, P=0.021) respectively and significantly higher in group III compared to group IV (p=0.001).

Conclusions: The novel triple combination injection was to be promising and long lasting for the suppression of symptoms related to keloids and hypertrophic scars.

Keywords: Triple Therapy, Interalesional Drug Monotherapy, Keloid, 5-fluorouracil, Triamcinolone, Hyaluronidase.

Introduction:

Wound healing may result in ordinary scar or hypertrophic scar which can be temporally grouped into three distinct phases (inflammation, proliferation, and remodeling [1]. Immediately following wounding, platelet degranulation and activation of the complement and clotting cascades form a fibrin clot for hemostasis, which acts as a scaffold for wound repair . Once the wound is closed, the immature scar transitions into the final maturation phase, where abundant extra cellular matrix is degraded and immature type III collagen is modified into mature type I collagen [2]. Characteristically, fresh scars appear reddish, sometimes itchy and slightly elevated, eventually turning to flat, frequently depigmented scars without further symptoms, within a period of months, The majority of scars fade at approximately 7 months [3].

Keloid is a type of scar with formation of either type III (early) or type I (late) collagen. It is a result of an overgrowth of granulation tissue (collagen type III) at the site of a healed skin injury which is then slowly replaced by collagen type I. Keloids are firm, rubbery lesions or often shiny fibrous and vary from single nodules to multiple linear plaques and can vary from pink to the color of the person's skin or red to dark brown in color. A keloid scar is benign and not contagious, but sometimes accompanied by severe itchiness, pain and changes in texture. In severe cases, it can affect movement of skin and hence limitation of limb movement if affect joint [4] .

Keloid also called benign fibro-proliferative scars as it grows beyond the confines of original wound and invade surrounding skin. It does not regress and tend to reoccur after excision [5].

The frequency of occurrence is 15 times higher in highly pigmented people. African descendant people have increased risk of keloid occurrence [1].

Keloids represent a therapeutic challenge. There is no universally accepted treatment resulting in permanent ablation of these scars [6]. The high recurrence rate has initiated a wide

variety of treatments, such as, compression therapy, intralesional injections of corticosteroid, 5-fluorouracil, methotrexate, bleomycin, radiotherapy, cryosurgery, laser therapy, tamoxifen, and tacrolimus [7].

The aim of this work was to evaluate clinically and microscopely the efficacy of intralesional triple therapy by 5-fluorouracil, triamcinolone acetonide and hyaluronidase versus intralesional injection of 5-fluorouracil and triamcinolone and Hyaluronidase each alone in treatment of Keloids.

Patients and Methods:

This prospective study was conducted at the Dermatology and Venereology Department in Tanta University Hospitals during the period between January 2018 till January 2019. The study was carried out on 40 patients who were diagnosed clinically and histologically as Keloid since at least 7 months duration and measuring more than 1 cm in size and had stopped treatment at least 3 months before enrolment in the study. An informed written consent was obtained from all cases before participating in the study, and after complete explanation of the advantages and disadvantages of the study. Also, the study was approved by the local ethical committee of Tanta University.

Patients who received treatment of keloid in the last 3 months before enrolment in the study, with kidney disease, liver disease, ischemic heart disease, neurological disease, endocrine disease, malignancy or any other systemic disease and pregnant or lactating women or those planning for pregnancy were excluded.

Patients were divided into 4 equal groups:

Group A: Patients were given triple intralesional therapy of total 1 ml solution of the combination by aspirating 0.6 ml 5- fluorouracil (250mg / 5ml) and 0.4 ml of Triamcinolone (40mg / ml) and vial containing a vacuum dried tablet of hyaluronidase 1500 units. The three agents were incorporated and shaken vigorously to assure adequate mixing of the

components. The mixture was then aspirated into 2ml syringe with an 18-gauge needle. Each 1 cm^2 from keloid was injected by 0.3 ml of the solution in the session which was planned for one-month interval. One average patient required five subsequent treatment sessions.

Group B: Patients were given intralesional of 5-fluorouracil (250mg / 5ml) and each 1 cm^2 of keloid was injected by 0.3 ml of the solution for one session monthly for five subsequent sessions.

Group C: Patients were given intralesional of triamcinolone (40mg / ml) and each 1 cm^2 of keloid was injected by 0.3 ml of the solution for one session monthly for five subsequent sessions.

Group D: Patients were given intra lesional of hyaluronidase 1500 units and each 1 cm^2 of keloid was injected by 0.3 ml of the solution for one Session monthly for five subsequent sessions.

All patients were be subjected to the following: Full history taking from the patient or his/her relatives [This is include age, sex and medical history including diabetes mellitus and hypertension], Clinical examination [General and dermatological], Examination the skin lesion [Onset, course, duration, morphology as regard site, size, surface, tenderness, itching and distribution of the lesions], Digital photography of the lesions will be taken before and after each injection at the end of treatment, Tissue punch biopsies from the lesional skin before and after therapy will be obtained and processed . Five μm sections will be stained by haematoxylin and eosin (H&E) stain to be examined by light microscope. Morphometric analysis will be carried out to compare the microscopic results before and after therapy.

Lesions had undergone objective evaluation using Vancouver Scar Scale (VSS). For VSS, keloid height was measured by centimetre scale, pliability was assessed by palpation, vascularity was assessed by visual inspection and pigmentation was scored after blanching and comparing it with the surrounding skin. Blanching was achieved using a piece of clear

plastic sheet. Three blinded dermatologist evaluation by comparing photos before and after treatment of the four group. Histopathological examination to tissue punch biopsies from the lesional skin before and after the therapy.

Clinical comparison was done by three blinded dermatologists between four groups of patients before and after treatment examination.

Light microscopic examination and morphometric analysis were carried by a histologist to compare the results from keloid before and after the therapy.

Statistical Analysis:

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test. Pearson correlation was done to estimate the degree of correlation between two quantitative variables. Linear Correlation coefficient (r) was used for detection of correlation between two quantitative variables in one group. A two tailed P value < 0.05 was considered statistically significant.

Results:

Demographic data, duration and size of lesion were statistically insignificant different among the groups. **[Error! Not a valid bookmark self-reference.]**

Table 1: Comparison between the different studied groups according to demographic data, duration, skin type and complication

	Group I (n = 10)	**Group II (n = 10)**	**Group III (n = 10)**	**Group IV (n = 10)**	**Test of Sig.**	**p**
	N (%)	**N (%)**	**N (%)**	**N (%)**		
Sex						

Male (24)	5(50.0)	6(60.0)	6(60.0)	7(70.0)	χ^2= 0.952	^{FE}p= 0.971
Female (26)	5(50.0)	4(40.0)	4(40.0)	3(30.0)		
Age (years)						
Min. – Max.	15.0 – 65.0	8.0 – 52.0	5.0 – 60.0	5.0 – 54.0	F= 1.051	0.382
Mean ± SD.	38.0 ± 17.46	26.70 ± 14.53	27.90 ± 17.70	28.0 ± 15.06		
Median (IQR)	34.50 (24.0 -52.0)	25.0 (18.0 – 33.0)	28.50 (13.0 – 38.0)	27.0 (18.0 – 38.0)		
Duration						
Min. – Max.	6.0 – 36.0	9.0 – 48.0	7.0 – 36.0	7.0 – 24.0	2.231	0.526
Mean ± SD.	19.20 ± 10.12	19.90 ± 11.49	17.40 ± 9.44	14.0 ± 6.55		
Median (IQR)	18.0 (12.0 – 24.0)	18.0 (12.0 – 24.0)	15.0 (9.0 – 24.0)	12.0 (8.0 – 18.0)		
Skin type						
III (36)	9(90.0%)	9(90.0%)	9(90.0%)	9(90.0%)	χ	^{FE}p
IV (4)	1(10.0%)	1(10.0%)	1(10.0%)	1(10.0%)		
Size (cm)						
Min. – Max.	2.0 – 11.0	2.0 – 4.0	2.0 – 10.0	2.0 – 7.0	4.415	0.220
Mean ± SD.	5.0 ± 2.72	2.85 ± 0.71	3.90 ± 2.44	3.60 ± 1.47		
Median (IQR)	4.75 (3.0 – 6.0)	3.0 (2. – 3.50)	3.0 (2.50 – 5.0)	3.25 (2.50 – 4.0)		
Complication	**N (%)**	**N (%)**	**N (%)**	**N (%)**		
	0(0)	10.(100)	10(100)	0(0)		

χ^2: Chi square test; FE: Fisher Exact; F: F for ANOVA test, p: p value for comparing between the studied groups, Data are represented by mean± SD and median, H: Kruskal Wallis test

There was no statistically significant difference among the studied groups regarding to cause, previous treatment and site. **[Error! Reference source not found.]**

Table 2: Comparison between the different studied groups according to cause, previous treatment and site

Cause	**Group I (n = 10)**	**Group II (n = 10)**	**Group III (n = 10)**	**Group IV (n = 10)**	χ^2	^{MC}p
	N (%)	**N (%)**	**N (%)**	**N (%)**		
Accidental Trauma (1)	1(10.0)	0(0.0)	0(0.0)	0(0.0)	9.282	0.743
Recurrence after Surgical removal (6)	2(20.0)	2(20.0)	0(0.0)	2(20.0)		
Burn (13)	3(30.0)	2(20.0)	4(40.0)	4(40.0)		
Spontaneous (8)	3(30.0)	2(20.0)	2(20.0)	1(10.0)		
Surgical Wound (12)	1(10.0)	4(40.0)	4(40.0)	3(30.0)		
Previous treatment						
No	2(20.0)	1(10.0)	3(30.0)	2(20.0)	7.806	0.936
Topical steroid	4(40.0)	6(60.0)	5(50.0)	5(50.0)		
Surgery &IL	1(10.0)	0(0.0)	0(0.0)	0(0.0)		
IL steroid	2(20.0)	3(30.0)	1(10.0)	3(30.0)		
Surgery	1(10.0)	0(0.0)	1(10.0)	0(0.0)		

Site						
Behind ear	1(10.0)	1(10.0)	1(10.0)	0(0.0)	1.551	1.000
Back	3(30.0)	2(20.0)	1(10.0)	1(10.0)	1.854	0.802
Lower limb	1(10.0)	1(10.0)	2(20.0)	2(20.0)	1.028	1.000
Upper limb	2(20.0)	3(30.0)	2(20.0)	4(40.0)	1.429	0.865
Nuchal area	1(10.0)	0(0.0)	1(10.0)	1(10.0)	1.551	1.000
Face	1(10.0)	1(10.0)	1(10.0)	1(10.0)	0.614	1.000
Chest	1(10.0)	2(20.0)	2(20.0)	0(0.0)	2.566	0.726
Neck	0(0.0)	0(0.0)	0(0.0)	1(10.0)	2.880	1.000

X^2: Chi square test; MC: Monte Carlo; p: p value for comparing between the studied groups

Thickness was highly statistically significant difference between groups after intervention (P =0.008) and was no statistically significant difference between four groups before intervention. Vancouver was highly statistically significant difference between groups after intervention (P <0.001) and was no statistically significant difference between four groups before intervention. **[**

Table 3

Table 3: Comparison between the different studied groups according to thickness and Vancouver

		Group I	Group II	Group III	Group IV	H	p
Thickness (mm)	**Before**	**(n = 10)**	**(n = 10)**	**(n = 10)**	**(n = 10)**		
	Min. – Max.	3.0 – 10.0	1.0 – 7.0	5.0 – 10.0	2.0 – 15.0	1.561	0.668
	Mean ± SD.	5.10 ± 2.38.	5.20 ± 1.69	6.20 ± 2.10	6.20 ± 3.65		
	Median (IQR)	5.0 (3.0 – 6.0)	5.0 (5.0 – 6.0)	5.0 (5.0 – 7.0)	5.0 (5.0 – 5.0)		
	After	**(n = 3)**	**(n = 9)**	**(n = 10)**	**(n = 9)**		
	Min. – Max.	1.0 – 2.0	3.0 – 5.0	2.0 – 10.0	1.0 – 7.0	11.924*	**0.008***
	Mean ± SD.	1.33 ± 0.58	4.22 ± 0.83	4.70 ± 2.45	2.56 ± 2.07		
	Median (IQR)	1.0 (1.0 – 1.50)	4.0 (4.0 – 5.0)	4.0 (3.0 – 5.0)	2.0 (1.0 – 2.0)		
Vancouver	**Before**	**(n = 10)**	**(n = 10)**	**(n = 10)**	**(n = 10)**		
	Min. – Max.	4.0 – 11.0	5.0 – 11.0	5.0 – 10.0	6.0 – 11.0	4.758	0.190
	Mean ± SD.	6.60 ± 2.22	6.80 ± 1.62	6.70 ± 1.64	7.70 ± 1.70		
	Median (IQR)	6.0 (5.0 – 7.0)	6.50 (6.0 – 7.0)	6.0 (6.0 – 7.0)	7.0 (7.0 – 9.0)		
	p_5	**0.109**	**0.011***	**0.011***	**0.007***		
	After	**(n = 10)**	**(n = 10)**	**(n = 10)**	**(n = 10)**		
	Min. – Max.	0.0 – 4.0	4.0 – 10.0	3.0 – 7.0	2.0 – 6.0	25.237*	**<0.001***
	Mean ± SD.	1.30 ± 1.34	6.60 ± 1.90	4.30 ± 1.34	3.90 ± 1.37		
	Median (IQR)	1.0 (0.0 – 2.0)	6.0 (6.0 – 6.0)	4.0 (3.0 – 5.0)	3.50 (3.0 – 5.0)		

Data are represented by mean± SD and median, *: Statistically significant at $p \leq 0.05$

There was no statistically significant difference between studied groups regarding pigmentation before and after, color, itching and pliability were no significant difference between groups before intervention while there was statistically significant difference between groups regarding color, itching and pliability after intervention. There was no statistically significant difference between groups regarding surface area of lesion. there was highly statistically significant difference between groups regarding General (NAD) (P<0.001). **[Table 4**

Table 4: Comparison between the different studied groups according to clinical data, pliability and surface area of keloids

		Group I (n = 10)	Group II (n = 10)	Group III (n = 10)	Group IV (n = 10)	χ^2	^{MC}p
		N (%)	N (%)	N (%)	N (%)		
Pigmentation	**Before**						
	Normal	8(80.0)	9(90.0)	9(90.0(	7(70.0)	.1.854	0.802
	Hyper	2(20.0)	1(10.0)	1(10.0)	3(30.0)		
	After						
	Normal	8(80.0)	8(80.0)	8(80.0)	7(70.0)	4.036	0.948
	Hyper	2(20.0)	2(20.0)	1(10.0)	3(30.0)		
	Hypo	0(0.0)	0(0.0)	1(10.0)	0(0.0)		
	p_1	**1.000**	**0.317**	**0.317**	**1.000**		
Color	**Before**						
	Normal	3(30.0)	0(0.0)	0(0.0)	0(0.0)	8.034	0.133
	Pink	5(50.0)	9(90.0)	9(90.0)	7(70.0)		
	Purple	2(20.0)	1(10.0)	1(10.0)	3(30.0)		
	After						
	Normal	7(70.0)	0(0.0)	1(10.0)	0(0.0)	19.549*	**<0.001***
	Pink	3(30.0)	7(70.0)	9(90.0)	8(80.0)		
	Purple	0(0.0)	3(30.0)	0(0.0)	2(20.0)		
	p_1	**0.014**	**0.157**	**0.157**	**0.564**		
Itching	**Before**						
	Yes	8(80.0)	10(100.0)	9(90.0)	7(70.0)	3.671	0.457
	After						
	Yes	0(0.0)	10(100.0)	9(90.0)	0(0.0)	39.727*	**<0.001***
	p_1	**0.008**	**–**	**1.000**	**0.016**		
Pliability	**Before**						
Firm		0(0.0)	9(90.0)	8(80.0)	9(90.0)	3.715	0.750
Supple		9(90.0)	1(10.0)	0(0.0)	0(0.0)		
Yeilding		1(10.0)	0(0.0)	2(20.0)	1(10.0)		
After							
Normal		10(100.0)	0(0.0)	3(30.0)	8(80.0)	29.189*	**<0.001***
Firm		0(0.0)	9(90.0)	0(0.0)	0(0.0)		
Supple		0(0.0)	1(10.0)	5(50.0)	1(10.0)		
Yeilding		0(0.0)	0(0.0)	2(20.0)	1(10.0)		
p_1		**0.001***	**1.000**	**0.683**	**0.127**		
Surface area		**Before treatment**					
Smooth		8(80.0)	6(60.0)	10(100.0)	7(70.0)		

Irregular	2(20.0)	4(40.0)	0(0.0)	3(30.0)	5.175	0.231
after treatment						
Smooth	8(80.0)	6(60.0)	10(100.0)	7(70.0)		
Irregular	2(20.0)	4(40.0)	0(0.0)	3(30.0)		
χ2 (P value)	**1**	**3.45 (0.45)**	**1**	**1**		
Other data						
Other cut	0(0.0)	0(0.0)	0(0.0)	0(0.0)		
General (NAD)	10(100.0)	10(100.0)	10(100.0)	10(100.0)	40.00	**<0.001***
Inves	0(0.0)	0(0.0)	0(0.0)	0(0.0)		

X^2: Chi square test, p: p value for comparing between the studied group, *: Statistically significant at $p \leq 0.05$

There was highly statistically significant difference between studied groups regarding both blind dermatologist and patient satisfaction (P<0.001). Blind dermatologist and patient satisfaction was significantly higher in group I compared to other three groups (P<0.05), was significantly lower in group II compared to group III and IV group (P=0.003, P=0.004, P=0.034, P=0.021) respectively and significantly higher in group III compared to group IV (p=0.001). Table 5

Table 5: Comparison between the different studied groups according to blind dermatologist and patient satisfaction

	Group I (n = 10)	**Group II (n = 10)**	**Group III (n = 10)**	**Group IV (n = 10)**	**H**	**p**
Blind dermatologist						
Min. – Max.	70.0 – 95.0	0.0 – 55.0	35.0 – 70.0	40.0 – 75.0		
Mean ± SD.	81.50 ± 7.84	14.50 ± 18.77	61.0 ± 14.68	50.0 ± 10.27	29.238*	**<0.001***
Median (IQR)	80.0 (80.0 – 85.0)	7.50 (0.0 – 20.0)	70.0 (45.0 – 70.0)	50.0 (40.0 – 50.0)		
p_1		**<0.001***	**0.020***	**0.001***		
Sig. bet. groups		p_2=0.003*, p_3=0.034*, p_4=0.380				
Patient satisfaction						
Min. – Max.	85.0 – 100.0	0.0 – 50.0	30.0 – 75.0	50.0 – 75.0		
Mean ± SD.	95.0 ± 5.27	16.50 ± 20.28	62.0 ± 17.83	59.0 ± 8.76	31.287*	**<0.001***
Median (IQR)	95.0 (90.0 -100.0)	7.50 (0.0 – 30.0)	70.0 (40.0 – 75.0)	60.0 (50.0 – 65.0)		
p_1		**<0.001***	**0.007***	**0.001***		
Sig. bet. groups		p_2=0.004*, p_3=0.021*, p_4=0.597				

H: H for Kruskal Wallis test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test), p: p value for comparing between the studied groups, p_1: p value for comparing between group I and each other group, p_2: p value for comparing between group II and group III, p_3: p value for comparing between group II and group IV, p_4: p value for comparing between group III and group IV, *: Statistically significant at $p \leq 0.05$

Discussion:

Keloids are some of the most troublesome of all benign growths on the human body to treat for clinicians. Those affected with keloids often consult dermatologists with symptoms of pain , pruritus and limitation of movment if it affects joint. In some cases of these skin lesions, they can be the cause of disharmony in both social and interpersonal relations. For these reasons, it is imperative that we find solutions to treat these lesions that resolve the symptoms and treat the actual lesions **[8].**

TAC is the most popular drug in keloid treatment alone or in combination. Shah et al.[9]**.** 5FU was first introduced in the treatment of keloid by Fitzpatrick who published his results in 1999. Fitzpatrick,[10] .Hyaluronidase, the third ingredient had been used for many years in intra abdominal surgical procedures ,ear , nose ,and throat surgical procedures and even in spinal surgeries to break through tough fibrous adhesions. [11].

The most common anatomical sites of keloids in present study were upper limbs followed by head and neck then the back ,the chest (presternal area) and behind ear . Unlike , Mouhari et al.,[12] noted that sternum, upper limb and head & neck were the most common sites for keoids in dark skin patients. That could be attributed to the tendency of keloids to occur on highly mobile sites with high tension such as shoulders, neck, and presternum [1]. Also , Conversely, Bayat et al., [13] reported that ear was the most common site for keloids.

The most common causes of keloids in present study were burn (32.5%), post surgical wound (30%) then followed by spontaneous appearance of keloid (20%) , recurrence after surgical removal (15%) and accidental trauma (2.5%). Our result go with Annabi et al.,[14] and Shaheen et al.,[15] who reported that the most common cause of keloids differs according to conditions of study's society. They found that keloids could follow any form of skin injury, but burns were the most common **.** Bayat et al. [13] found that trauma was the most common cause of keloids.

Dominance of complication in 5-FU group were supported by several studies Gupta and Kalra et al.,[16] , treated 24 consecutive patients with 50–150 mg intralesional injections of 50 mg/ml of 5-FU using 1-week injection intervals for a total of 16 injections. Clinical evaluation by a single observer was done at treatment, cessation of treatment, and the follow-up period. Side effects of treatment included pain and hyperpigmentation in all 24 patients as well as ulceration in 1 patient. Kontochristopoulus et al.[6] also investigated the effects of intralesional 5-FU in 20 patients with keloid lesions on various locations including the chest, back, extremities, and earlobes.. Weekly intralesional injections of 0.2–0.4 ml/cm^2 of (250 mg/ 5ml 5-FU) were administered over an average of seven sessions. They found that forty percent of patients had good improvement, and 5% had excellent improvement. At 52-week follow-up, 47% demonstrated reoccurrence. All patients experienced pain and transient hyperpigmentation, and six patients had superficial ulceration.

Triamcinolone acetonide has long been the steroid of choice for the injectional medicine in the treatment of hypertrophic scars and keloids. Most of the clinical research in the scar arena suggests that intralesional corticosteroids, alone, or in the form of combination, provide the best relief of local symptoms as well as flattening of the scars themselves. According to previous literature, the dosage of triamcinolone acetenoide for intralesional keloid injection has varied from 10 to 40 mg/mL, and the treatment is administrated at intervals of 4 to 6 weeks [17, 18].

Actually, the monotherapeutic use of intralesional TAC in keloids treatment has been shown to be effective but it might induce more side effects in the form of hypopigmentation, mixed pigmentation, fat atrophy, telangiectasias, necrosis and ulcerations [4, 19, 20]

Our result goes in aggrement with Prabhu et al.[7]which compared the efficacy of weekly intralesional injections of 50 mg/ml 5-FU versus 40 mg/ml TAC (control) in 30 patients with keloids for 4 weeks. They showed a good to excellent flattening of keloid size was seen in

64% of patients receiving 5-FU versus 87% in patients receiving TAC monotherapy, and the difference was statistically significant. More complications were encountered in the 5-FU group.

In the current study group (IV) had been given intra lesional injection of hyaluronidase 1500 units dissolved in 1 cm saline only and with an interval of 4 weeks between injections for 5 sessions and each 1 cm2 injected by 0.3 ml of solution . The results showed statistical significant difference (p_5 value = 0.004) but in group A which had been injected by triple combination showed high statistical significant difference ($p_5$value = 0.001) , three blinded dermatologist evaluation was 10% moderate , 60% mild and 30% poor and regarding patient satisfaction scale 60 % satisified and 40% dissatisified .

These results were in aggrement with Elvira-Ioana et al.,[21] who reported that hyaluronidase useful in the presence of single small scar or combined with corticosteroid therapy (in severe keloid scars) giving the best results. The most effective treatment was a combination of intralesional triamcinolone acetonide followed by hyaluronidase injection, used to complete the healing after corticosteroid therapy .

Several studies regarding combination of 5FU with TAC, Khan et al.[22] enrolled 150 patients to receive either intralesional 0.25 ml of 40 mg/ml TAC diluted with 0.75 ml normal saline or 0.9 ml of 50 mg/ml of 5-FU mixed with 0.1 ml of 40 mg/ml TAC. There was significant improvement with 5-FU/TAC compared to TAC monotherapy, with 63 FU/TAC patients (84%) having good to excellent results compared to 51 TAC patients (68%). There were no instances of scar recurrence at 6-month follow-up. Eighteen patients (24%) who were administered TAC alone and six patients (8%) who were given 5-FU/TAC experienced complications.

On the other hand Davidson et al. [23] conducted a retrospective review of 94 patients with 102 keloids. Keloids were separated into three treatment groups including: 5-FU/TAC

without excision (52 subjects), 5-FU/TAC with excision (24 subjects), and TAC treatment with excision (26 subjects). A 3:1 concentration of 37.5 mg/ml of 5-FU and 10 mg/ml of TAC was mixed, and 0.1 ml of solution per centimeter of lesion was injected. Excisional patients were given injections 2, 4, and 6 weeks after surgery, and non-excisional patients were administered injections every 4 weeks. A statistically significant reduction in keloid size was seen with 5FU/TAC regimens (92%) as compared to TAC alone (73%). Patients with keloids treated with 5-FU experienced pain and pruritus .

Recent study utilized another triple combination done by Aggarwal et al.,[24], which found that intralesional triamcinolone acetonide, intralesional triamcinolone acetonide with hyaluronidase, and intralesional radiofrequency with triamcinolone acetonide are effective modalities for the treatment of keloids. However, intralesional triamcinolone acetonide with hyaluronidase fares better than other two as far as safety is concerned with least side effects.

Conclusion

The novel triple combination injection has been shown in this clinical and microscopical evaluation to be promising and long lasting for the suppression of symptoms related to keloids and hypertrophic scars. In comparison to some surgical procedures and other modalities, this therapy is rather inexpensive, easily available, and an effective treatment option that can be offered in the consulting/treatment room.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med. 2011;17:113-25.

2. Slemp AE, Kirschner RE. Keloids and scars: a review of keloids and scars, their pathogenesis, risk factors, and management. Curr Opin Pediatr. 2006;18:396-402.

3. Gauglitz GG, Pavicic T. [Emerging strategies for the prevention and therapy of excessive scars]. MMW Fortschr Med. 2012;154:55-8.

4. Alster TS, Tanzi EL. Hypertrophic scars and keloids: etiology and management. Am J Clin Dermatol. 2003;4:235-43.

5. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. Plast Reconstr Surg. 2010;125:557-68.

6. Kontochristopoulos G, Stefanaki C, Panagiotopoulos A, Stefanaki K, Argyrakos T, Petridis A, et al. Intralesional 5-fluorouracil in the treatment of keloids: an open clinical and histopathologic study. J Am Acad Dermatol. 2005;52:474-9.

7. Prabhu A, Sreekar H, Powar R, Uppin V. A randomized controlled trial comparing the efficacy of intralesional 5-fluorouracil versus triamcinolone acetonide in the treatment of keloids. Journal of the Scientific Society. 2012;39:19.

8. Hietanen KE, Järvinen TA, Huhtala H, Tolonen TT, Kuokkanen HO, Kaartinen IS. Treatment of keloid scars with intralesional triamcinolone and 5-fluorouracil injections - a randomized controlled trial. J Plast Reconstr Aesthet Surg. 2019;72:4-11.

9. Shah VV, Aldahan AS, Mlacker S, Alsaidan M, Samarkandy S, Nouri K. 5-Fluorouracil in the Treatment of Keloids and Hypertrophic Scars: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb). 2016;6:169-83.

10. Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg. 1999;25:224-32.

11. Martín-Cartes J, Morales-Conde S, Suárez-Grau J, López-Bernal F, Bustos-Jiménez M, Cadet-Dussort H, et al. Use of hyaluronidase cream to prevent peritoneal adhesions in laparoscopic ventral hernia repair by means of intraperitoneal mesh fixation using spiral tacks. Surg Endosc. 2008;22:631-4.

12. Mouhari-Toure A, Saka B, Kombaté K, Akakpo S, Egbohou P, Tchangaï-Walla K, et al. Is There an Association between Keloids and Blood Groups? ISRN Dermatol. 2012;2012:750908.

13. Bayat A, Arscott G, Ollier WE, McGrouther DA, Ferguson MW. Keloid disease: clinical relevance of single versus multiple site scars. Br J Plast Surg. 2005;58:28-37.

14. Annabi N, Yue K, Tamayol A, Khademhosseini A. Elastic sealants for surgical applications. Eur J Pharm Biopharm. 2015;95:27-39.

15. Shaheen A, Khaddam J, Kesh F. Risk factors of keloids in Syrians. BMC Dermatol. 2016;16:13.

16. Gupta S, Kalra A. Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. Dermatology. 2002;204:130-2.

17. Mustoe TA, Cooter RD, Gold MH, Hobbs FD, Ramelet AA, Shakespeare PG, et al. International clinical recommendations on scar management. Plast Reconstr Surg. 2002;110:560-71.

18. Srivastava S, Patil AN, Prakash C, Kumari H. Comparison of Intralesional Triamcinolone Acetonide, 5-Fluorouracil, and Their Combination for the Treatment of Keloids. Adv Wound Care (New Rochelle). 2017;6:393-400.

19. Jones ME, McLane J, Adenegan R, Lee J, Ganzer CA. Advancing Keloid Treatment: A Novel Multimodal Approach to Ear Keloids. Dermatol Surg. 2017;43:1164-9.

20. Azzam EZ, Omar SS. Treatment of auricular keloids by triple combination therapy: Surgical excision, platelet-rich plasma, and cryosurgery. J Cosmet Dermatol. 2018;17:502-10.

21. Elvira-Ioana B, Alexandra PA, Sabina B, Ioana C, Rares-Calin B, George J, et al. HYALURONIDASE EFFICACY IN TREATING KELOID SCARS, A CASE REPORT. Acta Medica Marisiensis. 2019;65.

22. Khan MA, Bashir MM, Khan FA. Intralesional triamcinolone alone and in combination with 5-fluorouracil for the treatment of keloid and hypertrophic scars. J Pak Med Assoc. 2014;64:1003-7.

23. Davison SP, Dayan JH, Clemens MW, Sonni S, Wang A, Crane A. Efficacy of intralesional 5-fluorouracil and triamcinolone in the treatment of keloids. Aesthet Surg J. 2009;29:40-6.

24. Aggarwal A, Ravikumar BC, Vinay KN, Raghukumar S, Yashovardhana D. A comparative study of various modalities in the treatment of keloids. International journal of dermatology. 2018;57:1192-200.