



Survivin level in keloids before and after treatment with FK506 (tacrolimus) versus intralesional steroid injection, correlating its level with clinical and histopathological treatment outcome

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Abstract: Background: Survivin is one of the inhibitors of apoptosis proteins family (IAP) and its expression in keloid was significantly higher than in normal skin tissue. Tacrolimus (FK506) is a calcineurin phosphatase inhibitor inhibits synthesis of inflammatory cytokines produced by T- lymphocytes and induces apoptosis through caspase-3 activation. Intralesional steroid (IL) is a corner stone in keloid treatment. **Objectives:** To assess survivin level as antiapoptotic factor in keloid and to evaluate the therapeutic effect of topical tacrolimus compared to IL steroid clinically and immunohistochemically. **Patient and Methods:** forty keloid patients were included in this study, twenty were treated by intralesional steroid and twenty were treated by topical tacrolimus for three months. Survivin level was estimated in keloid tissue before and after treatment. **Results:** Our study showed statistically significant higher level in the dermal and epidermal survivin immunoeexpression (p-value <0.05) in the keloid tissue as compared to the normal skin tissue. There was a statistically significant decrease (p-value <0.05) in the dermal and epidermal survivin immunoeprssion as well as Vancouver Scar Scale (VSS) after treatment in both steroid and tacrolimus groups without significant difference between both modalities. Keloid improvement was higher in steroid group (45%) than in tacrolimus group (25%); however, there was no statistically significant difference in keloid improvement between both treatment groups. **Conclusion:** Survivin plays a role in pathogenesis of keloid. Topical tacrolimus showed therapeutic effect in keloid treatment, however ILsteroid is the corner stone treatment modality of keloid.

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Keywords: Keloid; Survivin; Tacrolimus (FK506); IL; Steroid.

1. Introduction

Keloids are benign disfiguring fibroproliferative skin tumors that can impair the quality of life in affected individuals. Keloid is one of the most challenging skin conditions to treat as there is no gold standard therapy for treatment (1).

Survivin is an inhibitor of apoptosis which is highly expressed in malignant tumors. Its functional role includes promotion of cell proliferation, inhibition of apoptosis and enhancement of tumor angiogenesis (2). Previous studies showed that survivin expression was significantly higher in keloids than in normal skin (3).

Tacrolimus (FK506) is one of natural macrolide immune- suppressant with 10-100 folds immunosuppressive activity as cyclosporin. Tacrolimus reduces proliferation and promotes apoptosis of hypertrophic scar fibroblasts by inhibiting the expression of survivin (4).

Intralesional steroid injection is one of the first-line options to treat keloid scars. Steroids reduce the synthesis of collagen, inhibit inflammatory mediators as transforming growth factor beta1 (TGF-β1) and vascular endothelial growth factor (VEGF) and alter extracellular matrix (ECM) components such as glycosaminoglycans (5).

Our study aimed to estimate survivin level in keloid and to evaluate the therapeutic effect of topical tacrolimus (FK506) on keloids immunohistochemically and clinically compared to intralesional steroid as a documented keloid treatment.

2. Patient and Methods

The Research Ethical Committee of the Faculty of Medicine, Fayoum University approved this study. Informed written consents were obtained from all patients before conducting the study.

This prospective study was carried out from January 2018 to January 2019. Forty patients with keloid attending the Dermatology Outpatient Clinic of Fayoum University hospitals were included in this study. Exclusion criteria of the study included: Pregnancy, any other skin or systemic diseases, patients received any systemic medications, hypertrophic scars and keloid treatment over the last 6 months. Full history and careful general and dermatological examinations were done. Biopsies from keloid were taken before and after treatment. Survivin level was measured in all biopsies by rabbit monoclonal [EPR2675] antibody to survivin (HRP) (abcam, USA, cat # ab194239). Morphometric study

of survivin was done using Leica Qwin 500 LTD image analyzer computer system (Cambridge, England), in Histology Department, Faculty of Medicine, Cairo University. Patients in both treatment groups were evaluated clinically by Vancouver scar scale (VSS) (Table 1) to estimate severity and improvement of keloid. Photos were taken before treatment (baseline) for each patient with **Nikon D3100** a digital camera (14.2 Megapixel DX-format CMOS Image sensor). Another set of photos were taken in after completion of therapy using the same camera settings, lighting, and patient positioning. Finally, patient and physician satisfaction were assessed.

Table 1: Vancouver scar score (Finlay et al., 2017).

Score for each clinical feature	0	1	2	3	4
Pliability	normal	Supple	Yielding	Firm	Adherent
Height	normal	1–2mm	3–4mm	5–6mm	>6mm
Vascularity	normal	pink	red	purple	-
Pigmentation	Skin colored	hypopigmentation	hyperpigmentation	-	-

Keloid patients were divided to two groups: group (A) included twenty patients received IL triamcinolone (TAC) (**Epirelefan 40 mg ampoule**) for three months with four weeks interval between sessions and group (B) included twenty patients received tacrolimus (**Tarolimus 0.03 mg**) twice per day, topically under occlusion for three months.

Statistical analysis

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using Statistical Package of Social Science (SPSS) software version 18 in windows 7. Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data. Quantitative data included in the study was first tested for normality by One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests were selected.

For quantitative parametric data: In-dependent student t-Test used to compare measures of two independent groups of quantitative data.

One way ANOVA test in comparing more than two independent groups of quantitative data with benferroni Post-HOC to test significance between each two groups. Paired t-test in comparing two dependent quantitative data.

For qualitative data:

Chi square test to compare two of more than two qualitative groups. Mc-Nemar test for paired dependent qualitative data. Bivariate Pearson correlation test to test association between variables. The p-value <0.05 was considered the cut-off value for significance.

3. Results

Our study included 40 keloid patients. Ages in both groups ranged between 3-56 years (mean \pm SD: 17.9 \pm 16.6). As regards sex distribution, in group A, 7 (35%) were males 13(65%) were females and in group B, 8 (40%) were males and 12 (60%) were females. There was a statistically significant decrease (p-value <0.05) in epidermal and dermal survivin level (Table. 2) as well as VSS (Table. 3) after treatment in both steroid and tacrolimus groups without significant difference between both modalities. Keloid improvement was higher in steroid group (45%) than in tacrolimus group (25%); however, there was no statistically significant difference in keloid improvement between both treatment groups. There was negative correlation between survivin level and age of the patients. However, there was no significant relation between survivin and other clinical data of patients, clinical findings or VSS. Both patient and physician satisfaction were statistically higher (p-value <0.05) among steroid group compared to tacrolimus group.

Table (2): Comparison between treatment groups regarding survivin level before and after treatment

Survivin level	Group A (n=20)		Group B (n=20)		p-value	Sig.
	Mean	SD	Mean	SD		
Epidermal Survivin level						
Before treatment	27.4	3.8	29.1	5.03	0.2	NS
After treatment	8.9	2.8	11.3	2.7	0.1	NS
P-value	<0.001		<0.001			
Dermal Survivin level						
Before treatment	22.3	4.1	22.8	5.3	0.9	NS
After treatment	8.3	2.2	9.2	2.6	0.2	NS
P-value	<0.001		<0.001			

Table (3): Comparison between treatment groups regarding VSS before and after treatment

VSS level	Steroid (n=20)		Tacrolimus (n=20)		p-value	Sig.
	Mean	SD	Mean	SD		
Before	7.6	1.8	6.5	1.1	0.01	S
After	4.3	1.4	4.8	1.4	0.3	NS
% of improvement	45%		25%		0.2	NS
p-value	<0.001		<0.001			
Sig.	HS		HS			

4. Discussion

Keloid, considered as dense fibrous tissue benign overgrowth, is one of the most complicated problems of the wound healing and no completely effective treatment is reached against these lesions till now (6). Survivin is a member of the inhibitor of apoptosis proteins (IAP) which exerts an anti-apoptotic effect by inhibiting the activity of caspase-3 (3).

Based on the current study, there was a significant negative correlation between survivin level and age of the patients. Decreased survivin level with progress of age may be coincidental event with the increased apoptosis in some aged cells. In support of our findings, it was reported that survivin can inhibit apoptosis by inhibition of caspases, then survivin inhibition is associated with apoptosis activation (7). Aging process is associated with disruptions in systemic and inter-cell signaling as well as mitochondrial malfunction resulting in increased apoptosis in some cell types, and decreased apoptosis in other cell types (8). On the contrary to our results, **Al-Khalaf and Aboussekhra** in 2013, documented that survivin immunoexpression increases with age and it supports the resistance of aged human fibroblasts to genotoxic stress and apoptosis (9).

Our study revealed that male-to-female ratio was 1:1.6 as males represented about one third and females represented about two thirds of all keloid cases in both treatment groups. Female patients with keloids presented to dermatology clinic seeking

treatment for the keloids more than males as they get worried about the disfigurement and need better cosmetic result after treatment. Also ear keloid after ear piercing in females was one of the common causes of keloid in our study patients. In agreement to our results, It was noted in previous studies that female patients were twice as prevalent as male patients (10), (11). Also **Belie et al**, in 2019 showed that male-to-female ratio in their study on keloid patients was 1:1.24 (12).

As regards the clinical therapeutic outcomes of IL steroid treatment in our study, there was a statistically significant improvement in clinical parameters (itching, tenderness, pliability, vascularity and height) before and after treatment with 65%, 30%, 80%, 47%, 50% keloid improvement respectively as steroids reduce the synthesis of collagen and alter ECM also inhibit inflammatory mediators included in keloid pathogenesis as VEGF and TGF- β 1. However, there was no statistically significant improvement in pigmentation with 15% improvement (table 4). In agreement with our results, it was reported that mean scar volumes are reduced from 0.73 \pm 0.701 mL to 0.14 \pm 0.302 mL after IL injections of TAC every month till clinical improvement was achieved (13). **Ogawa et al** in 2016 also reported that corticosteroid administration in keloids rapidly reduced the pain and itching and **Chua et al** in 2019 noticed flattening of 50– 100% of keloids and improvement of the erythema after IL injection of TAC suspension (14), (15).

As regards the clinical therapeutic outcomes of topical tacrolimus treatment in our study, there was statistically significant improvement in clinical parameters (itching, tenderness, pliability, vascularity and pigmentation) with 35%, 30%, 75%, 20%, 35% keloid improvement respectively due to immunosuppressive activity of tacrolimus which can inhibit inflammatory cytokines secreted from T lymphocytes. However, the height of the keloids showed no statistically significant decrease after treatment by topical tacrolimus with only 3% improvement (Table 5). **Berman et al** in **2017** supported our findings as they reported that most of patients with keloids who were treated with tacrolimus 0.1% ointment showed decreased keloid tenderness, erythema, pruritus and induration (**5**). **Veira et al** in **2010** reported also that intradermal tacrolimus reduced scar elevation index by 50% as compared with untreated lesions in a rabbit ear model (**16**).

Vancouver scar score (VSS) was chosen in our study for assessment of keloid severity. It was developed to describe pigmentation, vascularity, pliability and height of hypertrophic scars. In agreement to us, VSS was used for subjective evaluation of keloid scar before and after IL steroid treatment and it was documented that higher scores of VSS indicated greater pathology and severity of scars (**17**), (**18**).

Our results showed that there was a significant decrease in VSS after treatment in both steroid and tacrolimus groups. The improvement in most of clinical parameters in both treatment groups explains the decrease in VSS. Keloid improvement in steroid group (45%) was higher than in tacrolimus group (25%). However, there was no statistically significant difference in keloid improvement between steroid and tacrolimus groups after treatment which indicated that both treatment modalities achieved close, but not equal, clinical improvement and that IL steroid still has the upper hand in keloid treatment.

Table (4): Comparison of clinical data in group A before and after treatment

Variables	Clinical characters				% of improvement	p-value	Sig.
	Before		After				
	No.	%	No.	%			
Itching							
No	5	25%	18	90%	65%	<0.001	HS
Yes	15	75%	2	10%			
Tenderness							
No	13	65%	19	95%	30%	0.03	S
Yes	7	35%	1	5%			
Pliability							
Supple	0	0%	4	20%	80%	<0.001	HS
Yielding	0	0%	12	60%			
Firm	16	80%	4	20%			
Adherent	4	20%	0	0%			
Height							
Lesion height in mm	Mean	SD	Mean	SD	47%	0.001	HS
	3.4	0.9	1.8	1.1			
Vascularity							
Normal	2	10%	12	60%	50%	<0.001	HS
Pink	11	55%	8	40%			
Red	7	35%	0	0%			
Pigmentation							
Normal	10	50%	10	50%	15%	0.1	NS
Hypo	1	5%	6	30%			
Hyper	9	45%	4	20%			

Table (5): Comparison of clinical data in group B before and after treatment

Variables	Clinical characters				% of improvement	p-value	Sig.
	Before		After				
	No.	%	No.	%			
Itching							
No	11	55%	18	90%	35%	0.01	S
Yes	9	45%	2	10%			
Tenderness							
No	14	70%	20	100%	30%	0.01	S
Yes	6	30%	0	0%			
Pliability							
Yielding	0	0%	15	75%	75%	<0.001	HS
Firm	20	100%	5	25%			
Height							
Lesion height in mm	Mean	SD	Mean	SD	3%	0.2	NS
		2.8	0.8	2.7			
Vascularity							
Normal	10	50%	14	70%	20%	0.01	S
Pink	5	25%	5	25%			
Red	5	25%	1	5%			
Pigmentation							
Normal	5	25%	12	60%	35%	0.03	S
Hypo	8	40%	4	20%			
Hyper	7	35%	4	20%			

In the current study, 50% of the patients in steroid group had complications after treatment in the form of atrophy, telangiectasia or hypopigmentation. In agreement with our findings, Common IL steroid adverse effects reported were telangiectasia, atrophy and pigmentary changes as hyper- and hypopigmentation (15),(5).

Complication after topical tacrolimus observed in our study was just transient stinging sensation only in one third (30%) of patients in tacrolimus group. In support of our findings, it was reported that the most common adverse effect of topical tacrolimus is stinging or burning sensation which was transient (19), (20).

Based on our results, there was a statistically significant decrease in epidermal and dermal survivin levels after treatment in both steroid and tacrolimus groups. This indicated a similar effect of tacrolimus and steroid as anti survivin factors. In support of our findings, Syed et al in 2013 reported that IL triamcinolone injection significantly downregulated survivin in keloid fibroblasts (21). Regarding topical tacrolimus, Wang et al reported that tacrolimus can be used as a treatment of supra corneal hypertrophic scar after glaucoma surgery by inhibiting the expression of survivin, thus inhibiting proliferation and inducing apoptosis of fibroblasts. Fibroblasts from hypertrophic post glaucoma scar in rabbits'

eyes were cultured and locally treated by tacrolimus to evaluate its effect on survivin (4). Finally, there was no statistically significant relation between survivin level and VSS or clinical parameters before and after treatment in the present study.

Patient's satisfaction (poor, fair, good and excellent) in current study was significantly higher in steroid group compared to tacrolimus group. Patient's satisfaction was based mainly on changes in size, pliability and itching of keloid lesions and so our patients in steroid group noticed remarkable improvement mainly in the height, pliability, tenderness and itching, on the contrary, tacrolimus group patients showed very minimal improvement in the height although there was noticeable improvement in the pliability, itching and tenderness. This correlated with Draaijer et al point of view as they demonstrated that the patient's opinion of scars was influenced primarily by pruritus and thickness of scar (22).

Regarding physician satisfaction, there was a statistically significant difference between both steroid and tacrolimus groups with higher physician satisfaction in steroid group. Physician satisfaction depended on the change in complaints (size, tenderness, itching and disfigurement), clinical findings and if there were complications of the treatment or not. Finally, physician satisfaction is

considered to be a multifactorial evaluation unlike patient satisfaction. Similarly, **Kim et al in 2015** recorded any complications of treatment and significant changes that had occurred (decreased

subjective symptoms of pain and pruritus, changes in texture, hardness and height) after IL steroid and IPL (intense pulsed light) combined treatment for keloid to evaluate physician satisfaction level (23).

Cases

Group A

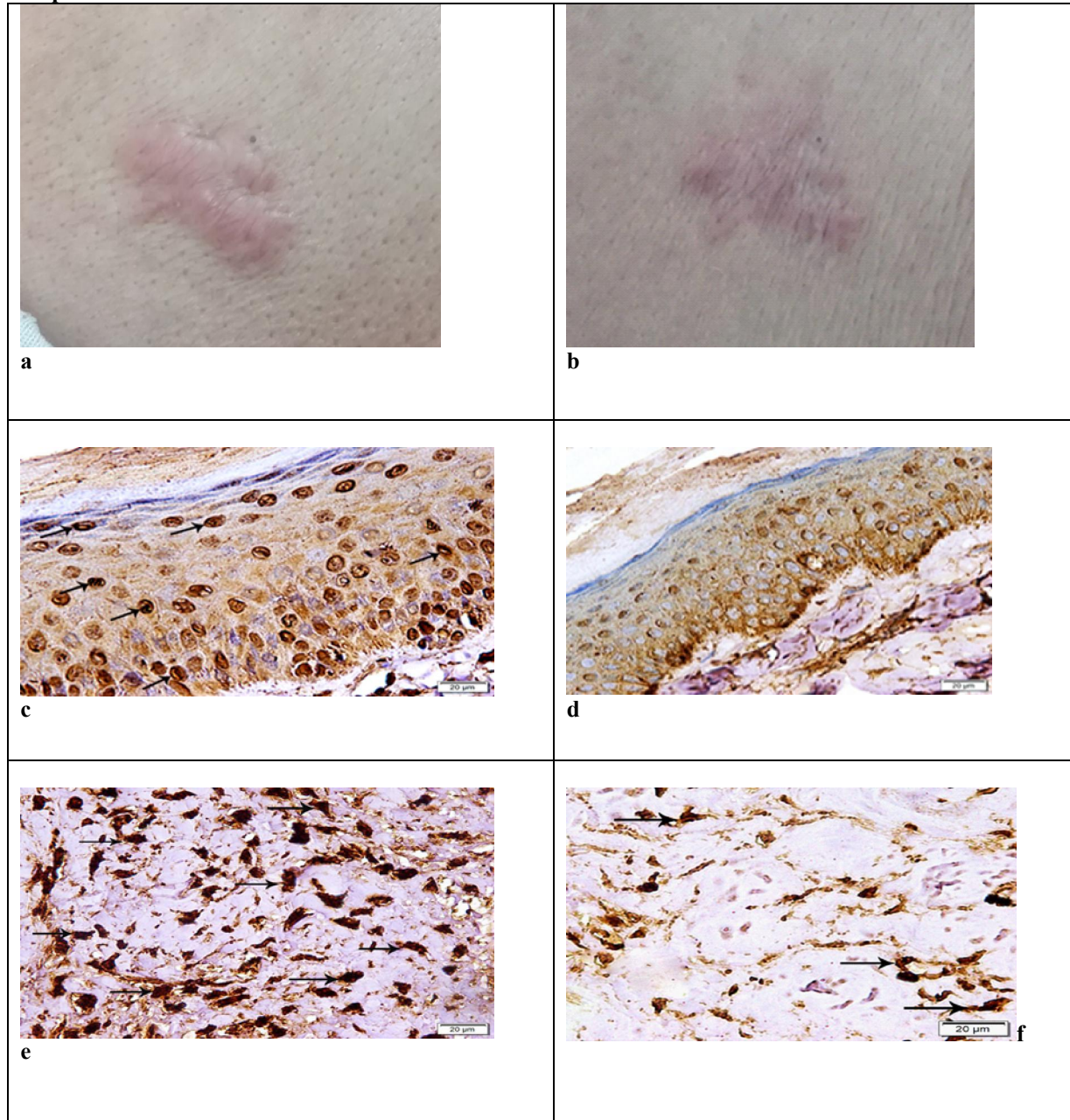


Figure 1: Case with keloid on the back (a) before and (b) after IL steroid treatment with excellent response. (c, e) Survivin immunohistochemical staining in epidermis and dermis respectively before IL steroid with numerous +ve nuclear survivin immunoreaction in all layers of the epidermis and in the dermal fibroblasts (arrows). (d, f) Survivin immunohistochemical staining after IL steroid treatment in epidermis and dermis respectively. The epidermis illustrating +ve cytoplasmic survivin immunoreaction in the basal cells and some nuclear survivin were noted in some suprabasal cells (arrows) and few +ve survivin immunostained fibroblast scattered in the dermis (arrows).

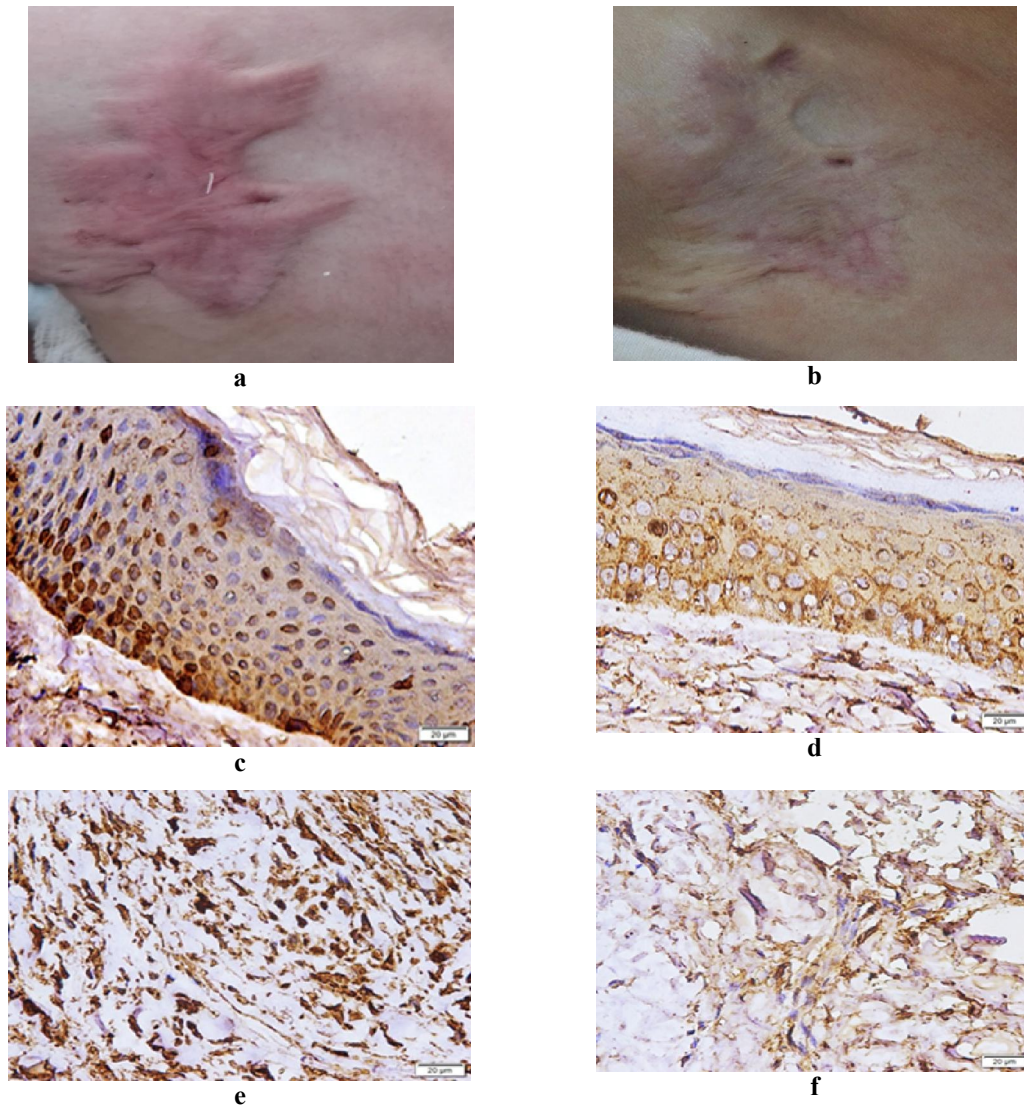


Figure 2: Case with keloid on the shoulder before (a) and after (b) IL steroid treatment with good response. (c, e) Survivin immunohistochemical staining in epidermis and dermis respectively before IL steroid treatment with numerous +ve nuclear survivin immunoreaction in epidermis and dermal fibroblasts. (d, f) Survivin immunohistochemical staining after IL steroid treatment in epidermis and dermis respectively with few +ve survivin immunostained epidermal cells and dermal fibroblasts.

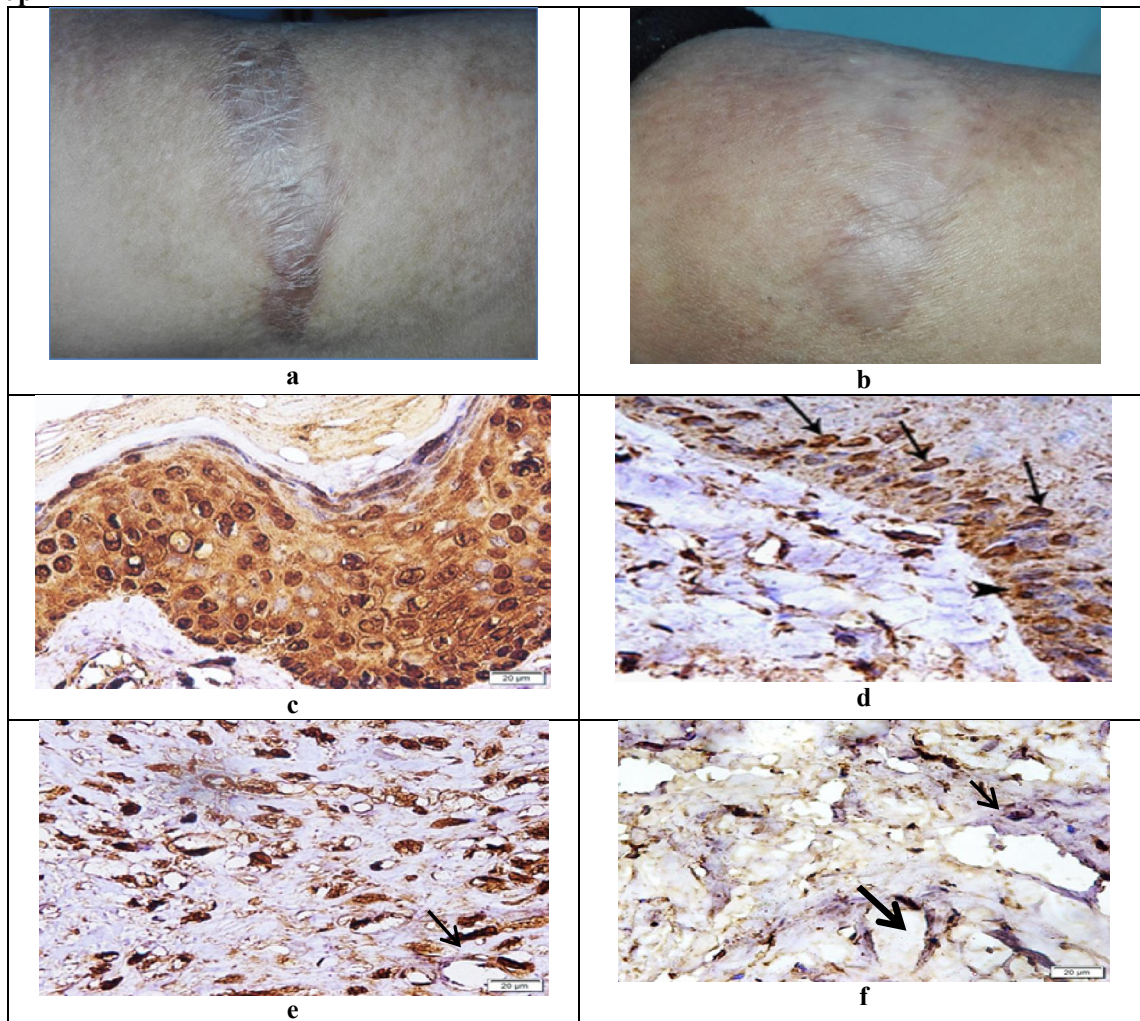
Group B

Figure 3: Case with keloid on the forearm before (a) and after (b) topical tacrolimus treatment with excellent response. (c, e) Survivin immunohistochemical staining in epidermis and dermis respectively before topical tacrolimus with numerous +ve nuclear survivin immunoreaction in all layers of the epidermis and in the dermal fibroblasts (arrows). (d, f) Survivin immunohistochemical staining after topical tacrolimus treatment in epidermis and dermis respectively with cytoplasmic and nuclear +ve survivin immunoreaction in basal and some suprabasal cells in the epidermis and fewer +ve survivin immunostained fibroblasts scattered in the dermis (arrows).

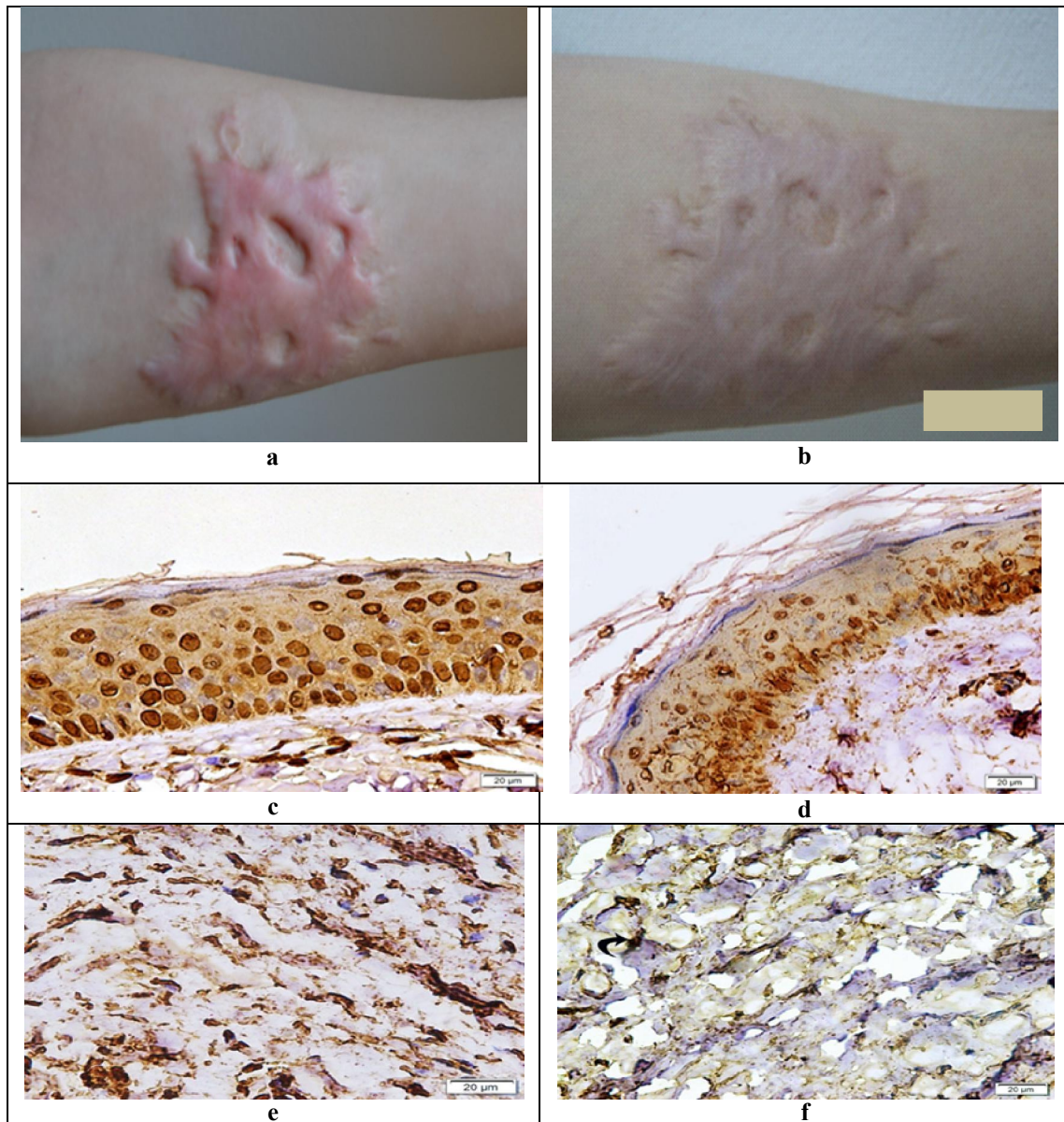


Figure 4: Case with keloid on the forearm before (a) and after (b) topical tacrolimus treatment with good response. (c, e) Survivin immunohistochemical staining in epidermis and dermis respectively before topical tacrolimus with numerous +ve nuclear survivin immunoreaction in all layers of the epidermis and in the dermal fibroblasts (arrows). (d, f) Survivin immunohistochemical staining after topical tacrolimus treatment in epidermis and dermis respectively with cytoplasmic and nuclear +ve survivin immunoreaction in basal and some suprabasal cells in the epidermis and fewer +ve survivin immunostained fibroblasts scattered in the dermis (arrows).

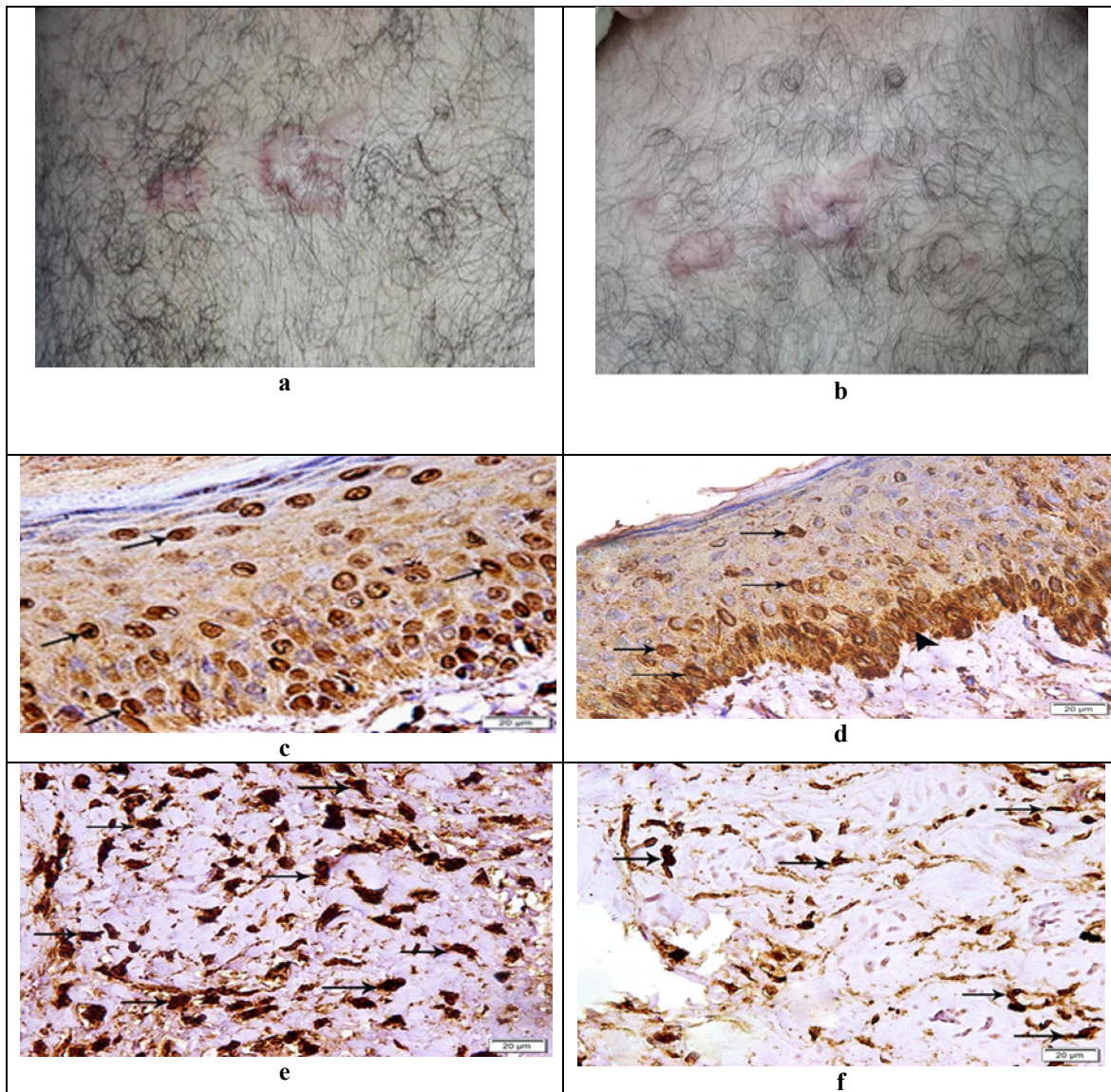


Figure 5: Case with keloid on the chest before (a) and after (b) topical tacrolimus treatment with fair response. (c, e) Survivin immunohistochemical staining in epidermis and dermis respectively before topical tacrolimus. (d, f) Survivin immunohistochemical staining after topical tacrolimus treatment in epidermis and dermis respectively.

Conclusion

We concluded that both IL steroid and topical tacrolimus have anti-survivin effect. Topical tacrolimus showed therapeutic effect in keloid treatment clinically and immunohistochemically, however, more satisfying results were achieved by IL steroid and more controlled studies are required for further validation of the results.

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