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Study the efficacy of intralesional pentoxifylline versus triamcinolone acetonide in keloid scars patients

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***Abstract*---**Keloids are prevalent fibro-proliferative tumors, and treating them is still a challenge although intralesional injections of triamcinolone acetonide (TAC) are effective, they have frequently linked adverse effects. Pentoxifylline (PTX) is an anti-fibrotic and anti-inflammatory, and vasodilator. It has not yet been tested for intralesional injection in keloids. The aim of the study is to study the efficacy of intralesional pentoxifylline versus triamcinolone acetonide in keloid scars of 40 patients. In this study, 40 patients with keloid scars regardless of the cause of keloid born, 20 patients have injected with intralesional triamcinolone acetonide, and 20 patients with intralesional pentoxifylline every two weeks until the lesion flatted or a maximum 6 sessions. Evaluation of Patient response to treatment was done by utilizing the verbal rating scale and Vancouver scar scale. Between groups A& B there is no statistically significant difference in height, color, the surface of the keloid, pigmentation consistency, verbal rating scale, visual analog scale (improvement in keloid), patient satisfaction, and several sessions for best results. There were no connections that are statistically significant between improvement on the Vancouver scar scale and age, the height of the keloid, and duration of the keloid scars and there were no statistically significantly different between the group B and group A. to verify our conclusions and assess the effectiveness of intralesional injection pentoxifylline, alone or in addition to other regular modalities being injected, can helps with keloid treatment or keloid scar prevention,

There is a need for trials with larger sample sizes and longer follow-up periods.

Keyword---Keloid, intralesional pentoxifylline, intralesional triamcinolone acetonide.

1-Introduction

The keloid is an irregular proliferation of the scar tissues that can form the area of cutaneous damage (for example, near to the site of a trauma or surgical incision); keloid scars do never retreat & expand besides the original scar boundaries. Keloid scars are distinct from hypertrophic scars, which are elevated scars that may fade with time and do not extend beyond the original wound's limits. (Atiyeh BS, Costagliola M, and Hayek SN,2005; Carswell L, Borger,2021) Keloid scars are caused by the shift in the usual equilibrium between wound healing degradation and extracellular matrix (ECM) deposition, particularly during the remodeling phase. (Butler PD, Longaker MT, and Yang GP,2008;Salem A, Assaf M, Helmy A,2009)

Keloid can result in severe deformity as well as signs such as pruritus, irritation, and pain. (Bayat A, McGrouther D, Ferguson M,2003) these manifestations include most prominent at the beginning of keloid formation, however, they are also present in some long-lasting keloid scars. (Bayat A, McGrouther DA,2005) Keloid scars might take months to occur, whereas raised scars normally appear within weeks of the original incident. Keloids and hypertrophic scars can affect people of all races and ages, but they are more common in people with darker skin. In African-Americans, keloids have been reported to be as high as 16 percent.

Keloids are less common among the elderly and the young. It affects people ranging in age from ten to thirty years old. In some people, a genetic predisposition combined with an important factor results in the production of a keloid scar. Many factors influence the severity of the hypertrophic scar and keloid formation, including depth, anatomic location, severity, tensional stress, environmental factors, the nature of injury infection, and genetic susceptibility. The pathophysiology of this disease is unknown. Recent research has linked transforming growth factor- (TGF-) and platelet-derived growth factor (PDGF) to the disease. In skin fibroblasts, they serve the function of adjusting contractile forces. Understanding wound healing plays a vital part in the etiology of keloid formation. Inflammatory, proliferative/fibroblastic, and maturation/remodeling are the three basic phases of wound healing.

A quick influx of inflammatory mediators into the affected location can occur during the inflammatory phase. During this stage, a fibrin clot forms. This happens as a result of capillary dilatation and mediator delivery. The fibroblastic phase involves the progression of fibroblasts into the fibrin clot, which leads to the production of new collagen. The wound matures through collagen synthesis and breakdown throughout the maturation period. This process is regulated by signaling molecules (PDGF, TGF-, matrix tissue inhibitors of metalloproteinases

[TIMPs], metalloproteinases [MMPs]). We can comprehend the pathogenesis of keloid or hypertrophic scars by understanding the wound healing process. In keloids, early forms of fibroblasts have been observed to remain longer than in normal skin. Collagen production rises as the shape of early fibroblasts changes. Keloids have a higher rate of collagen synthesis than normal skin. The primary form of collagen in normal skin types I, whereas keloids have both types I and III. The growth factor TGF- encourages fibroblasts to localize at sites of inflammation to begin the keloid process. Extracellular matrix protein synthesis is switched off in wound repair, and deregulation of TGF- activity is a key factor in keloid formation. Reduced synthesis of chemicals that cause collagen matrix breakdown (MMPs) has also been linked to collagen matrix breakdown a key element in the etiology of keloid lesions.

Infrared light has been proven to suppress fibroblast activity and proliferation in some investigations. CO2 laser excision of keloids has been demonstrated to be effective in several studies. (Robert Baran et al.,2017). There are various approaches to keloid treatment, but none are universally effective. Modification of collagen metabolism, modulation of the inflammatory response, and surgical and manual manipulation of the keloid scar are the three current treatment options. Cryotherapy, surgical excision, Irradiation, retinoids, tacrolimus, pulsed-dye laser therapy, fractionated CO2 laser therapy, silicone sheet dressings, and imiquimod and combination medications are just a few of the available treatments. Other options include intralesional injections of Verapamil, 5-fluorouracil, and steroids. (Trisliana Perdanasari et al.,2014)

Because surgical excision of keloid has a high rate of recurrence, For the first therapy, nonsurgical therapies are recommended. injection of steroids intralesionally, either alone or in combination with other drugs., is the most prevalent therapy. The most often used intralesional corticosteroid is triamcinolone acetonide (TAC).Keloids are still best treated with intralesional injections. Triamcinolone acetonide is the most prevalent medication. There are several different injectable concentrations of triamcinolone acetonide. The most frequent stock concentrations are 10 mg/mL and 40 mg/mL, with other dilutions easily generated by diluting these stock concentrations. Lidocaine is the most common diluent used to achieve local anesthetic at the injection site. Depending on the size and location of the keloid, the dose, and concentration change. A syringe with a smaller diameter provides a mechanical advantage for injection. It's best to use a 1-cc tuberculin syringe with a lure lock tip and a 27-gauge or bigger needle. (Robert Baran et al.,2017)

Because of the negative effects of corticosteroids, we will investigate the efficacy of intralesional pentoxifylline versus triamcinolone acetonide (TAC) in the current study. Pentoxifylline is used to reduce the side effects of corticosteroids. Pentoxifylline is a methyl-xanthine derivative that has immunomodulatory properties helps to reduce inflammation. Pentoxifylline is a drug that can be used to treat both dermatological and non-dermatological problems. It is a safe and reasonably priced medicine that has been utilized as both a main and adjuvant treatment. It can be used to treat keloids, scleroderma, hypertrophic scars, morphea, and other fibrosing conditions by inhibiting the proliferation and biosynthesis of fibroblasts produced from human skin.

The medication improves the deformability and chemotaxis of leukocytes. It inhibits neutrophil degranulation and inhibits endothelial leukocyte adhesion. Pentoxifylline reduces the susceptibility of leukocytes to cytokines and inhibits the generation of inflammatory cytokines. (Zhang M et al.,2004)

Pentoxifylline works by lowering blood viscosity and improving red blood cell deformability, allowing more blood to flow through partially blocked areas. (Bertram G.Katzung, Anthony J.Trevor 2015) Pentoxifylline has been shown to help with fibrosis problems. In high-risk patients, Post-surgical keloid recurrence was decreased by oral pentoxifylline (400 mg TID). (Tan A, Martinez Luna O, Glass DA,2020)

This study's objective was to measure the effectiveness of intralesional pentoxifylline injections against triamcinolone acetonide injections. Patients must be without any other treatment in the preceding month. Pregnant women and nursing mothers were not included in the study. Patients with kidney disease, as well as those allergic to theophylline, theobromine, and beverages with caffeine (coffee, tea, and colas) were excluded from the study. Patients who were planning any future surgery, those who were using drugs that prevent clotting (blood thinners), like warfarin and heparin, people who had a hemorrhage in their retina or brain, and those who had a risk factor for bleeding were excluded from all. (Mustoe TA,2002). Corticosteroids cause keloid regression through a variety of mechanisms. First, they have an anti-inflammatory action by preventing the movement and phagocytosis of leukocytes and monocytes. Second, they have a vasoconstrictor action, which lowers the amount of nutrients and oxygen delivered to the injury site. Finally, they possess anti-mitotic impact, inhibiting fibroblasts and keratinocytes, limiting re-epithelialization and the creation of new collagen. They may additionally decrease plasma protease inhibitors, facilitating collagen degradation by collagenase more quickly. (Roques C, Tèot L AC,2008). This caused alpha-1-antitrypsin and alpha-2-macroglobulin levels to rise, which are associated with the formation of keloid tissue and block collagenase in human skin. (Leventhal D, Furr M, and Reiter D ,2006).In scar tissues treated with corticosteroids, there was a drop in transforming growth factor(TGF), or insulin-like growth factor-1 (IGF-1), and hydroxyproline, indicating that corticosteroids impact fibroblast synthesis and proliferation and are responsible for their degeneration. (Carroll LA et al.,2002)

Because of the many negative effects of corticosteroids, such as atrophy, skin thinning, capillary dilatation, acne development, relatively high recurrence rates, hypopigmentation, ulcer formation, and Cushing syndrome, several trials are being done to replace them in keloid scars.

2-Method and Material

In this study with 40 patients with keloid scars regardless of the cause of keloid born, we injected 20 patients with intralesional triamcinolone acetonide and 20 with intralesional pentoxifylline in Baghdad teaching hospital department of dermatology and venereology, their age range between 6-60 years and the duration of study in one year the 40 patient in our study some had previously failed and ineffective treatment and some received treatment for first .pregnant

women, lactating mother, patients were allergic to products contain caffeine, patients with kidney disease, liver disease, patients taking anticoagulants drugs and those with risk of bleeding were excluded in the study we entered a preoperative assessment of keloid that includes site, cause, duration if the patient received previous treatment, height color, pigmentation, consistency, the surface of keloid, and the How many sessions are necessary for the best results, with patient satisfaction. we used triamcinolone acetonide vial (kenacort) 40mg/ml in 20 patients we take 1cc and diluted with lidocaine ampule and we used pentoxifylline ampule(trentilin) 100mg/5ml and we take 1cc and diluted with lidocaine, the trial grouping and also the sort of treatment blinded to the patient, the lesion blanching is the end point of the injection.

The patients were injected with an intralesional syringe every two weeks until the lesion flatted or a maximum of 6 sessions using an insulin syringe with 23-gauge, photographs were taken before and after the therapy to test the patient's response to the treatment. Evaluation of Patient response to treatment was performed by using a verbal rating scale(Breivik EK, Björnsson GA, and Skovlund E,2000) and Vancouver scar scale (Sullivan T et al.,1990)

Results and Discussions

With the use of IBM® SPSS version 26, data was analyzed. The numerical data were displayed using the standard deviation (SD) and mean, and the data's normality was examined using a one-sample Kolmogorov-Smirnov test, we presented categorical data as numbers and percentages. we compared two means in the same group by using the Wilcoxon test before and after treatment, and the relation between the significance and numerical variables among groups was tested by using the Kruskal-Wallis test. The qualitative data were compared using the chi-square test. Positive and negative associations between different variables were done by using linear correlation analysis.

Results

The characteristics of patients summarized in table 1

Table 1 Patient Characteristics

	Triamcinolone acteonide group A Number=20	Pentoxifylline group B Number=20	significance test	P-value
Age mean sd	 31.25 16.56	 29.2 **15**.8	K=0.545	0.460
Gender % Male female	 20%(4) 80%(16)	 40%(8) 60%(12)	X^2 = 2.552	0.11
keloid formation site % chest back	 10%(2) 5%(1)	 5%(1) 10%(2)	X^2 = 36.987	0.001

upper limb lower limp neck &head abdomen	25%(5) 20%(4) 35%(7) 5%(1)	30%(6) 0 55%(11) 0		
keloid duration \month Mean sd	 14.50 10.74	 16.95 25.28	K=0.305	0.581
The source of keloid % Wound Spontaneously Burning Trauma Vaccination Piercing of ear infection	 5%(1) (0) 50%(10) 10%(2) 0 25%(5) 10%(2)	 10%(2) 0 40%(8) 0 0 30%(6) 20%(4)	X^{2} =13.917	0.306
Past therapy received % Topical cream Laser therapy Surgical removal Intralesional 5-fu No therapy	 20%(4) 5%(1) 0 0 75%(15)	 0 0 10%(2) 10%(2) 80%(16)	X^{2} =11.063	0.026

Table 2 Treatment Results

	TAC group A (number=20)	PNT group B (number=20)	significance test	P- value
Keloid thickness (mm) Before the treatment Range Mean SD After the treatment Range Mean SD	 1-10 3.9 2.78 0.5-5 1.92 1.65	 1-5 2.85 1.53 0-5 1.75 1.43	K=1.515	P=0.218
P- value of the change in keloid thickness after treatment(z test)	0.000	0.000	K=0.027	P=0.870

Keloid Pigmentation Before the treatment Normal % Hyperpigmentation % Hypopigmentation % After the treatment Normal % Hyperpigmentation % Hypopigmentation % P- value of change in keloid pigmentation after treatment(friedman test)	 5%(1) 85%(17) 10%(2) 10%(2) 85%(17) 5%(1) 0.157	 25%(5) 75%(15) 0 40%(8) 60%(12) 0 0.083	 X^2 =3.686 X^2 =3.824	 P=0.158 P=0.148
Keloid Color Before the treatment Normal % Pink %% red % purple % After the treatment Normal % Pink %% Purple % Red % p -value of the change in color after the treatment	 10%(2) 30%(6) 0 60%(12) 20%(4) 35%(7) 15%(3) 30%(6) P=0.527	 25%(5) 40%(8) 15%(3) 20%(4) 35%(7) 25%(5) 20%(4) 20%(4) P=0.739	 X^2 =5.875 X^2 =13.745	 P=0.437 P=0.132
Keloid Consistency Before the treatment Normal % Supple % Firm% Band % Yielding % After the treatment Normal %	 0 40%(8) 45(9) 10%(2) 5%(1) 0	 0 35%(7) 50(10) 5%(1) 10%(2) 5%(1)	 X^2 = 7.956	 P=0.539

Supple % Firm% Band % Yielding %	50%(10) 15(3) 20%(4) 15%(3)	35%(7) 25%(5) 5%(1) 30%(6)		
P- value of the change in consistency after the treatment	P=0.391	P=0.105	X^{2} =10.473	P=0.575
Keloid Surface Before the treatment Smooth % Rough % Irregular %	 75%(15) 0 25%(5)	 75%(15) 5%(1) 20%(4)	X^{2} =5.422	P=0.066
After the treatment Smooth % Rough % Irregular % Depressed %	 50%(10) 0 0 50%(10)	 65%(13) 5%(1) 5%(1) 25%(5)		
P value of change in surface after the treatment(friedman test)	P=0.002	P=0.48	X^{2} =4.492	P=0.213
Satisfaction of patients % Yes No	 75%(15) 25%(5)	 45%(9) 55(11)	K=3.656	P=0.056
Number of sessions required for best result Range Mean SD	 3-6 4.85 1.04	 3-6 5.4 0.99	K=5.737	P=0.017

NOTE K for Kruskal-Wallis, X^{2} for Chi-square, Z for Wilcoxon, *Statistical significance is defined as p< 0.05.PNT(pentoxifylline),TAC(triamcinolone acetonide).

Table 3 Verbal rating scale

Verbal rating scale (VRS) n%	Triamcinolone acetonide Number=20	Pentoxifylline group Number=20	Significance test	P- value
Before the treatment				
No pain	5%(1)	10%(2)		
Mild pain	30%(6)	10%(2)	X^2 =1.556	P=0.956
Moderate pain	65%(13)	75%(15)		
Severe pain	0	5%(1)		
after the treatment				
No pain	15%(3)	10%(2)	X^2 =2.222	P=0.392
Mild pain	75%(15)	90%(18)		
Moderate pain	10%(2)	0		
Severe pain	0	0		
P value	0.000	0.000		

Table 4 Visual analogue scale

Visual analogue scale n%	Triamcinolone acetonide (number=20)	Pentoxifylline group (number=20)	Significance test	P- value
No change	0	10%(2)		
Weak response	0	30%(6)		
Mild response	40%(8)	10%(2)		
Moderate response	25%(5)	30%(6)		
Good response	25%(5)	15%(3)		
Excellent response	10%(2)	5%(1)		
P value	0.003	0.026	X^2 =13.917	P=0.532

No statistically correlations in age, gender, duration of keloid, cause of keloid, and site of keloid between two groups A and B. There is a significant statistically difference in past treatment received p-value equal to 0.003 Between different groups (p-value < 0.05).with group A there is a significant statistically difference in thickness of keloid, the surface of Keloid, improvement verbal rating scale and visual analog scale before & after treatment of triamcinolone acetonide, there is no statistically significant difference in group A pigmentation, color and consistency before and after treatment. with group B there is a significant statistically difference in thickness, verbal rating scale after treatment of pentoxifylline and visual analog scale (improvement in keloid).there is no statistically significant difference in the surface ,pigmentation ,color ,consistency

and keloid surface before and after treatment of pentoxifylline. between groups A& B there is no statistically significant difference in height, color, the surface of the keloid, pigmentation consistency, verbal rating scale, visual analog scale (improvement in keloid), or patient satisfaction. There were no statistically significant discovered relationships between improvement of VSS and age, the thickness of the keloid, and duration of keloid scars and groups A and B did not statistically differ from each other, however there were statistically significant correlations in a number of sessions for the best possible result (p-value equal to 0.017)

Table 5 side effects

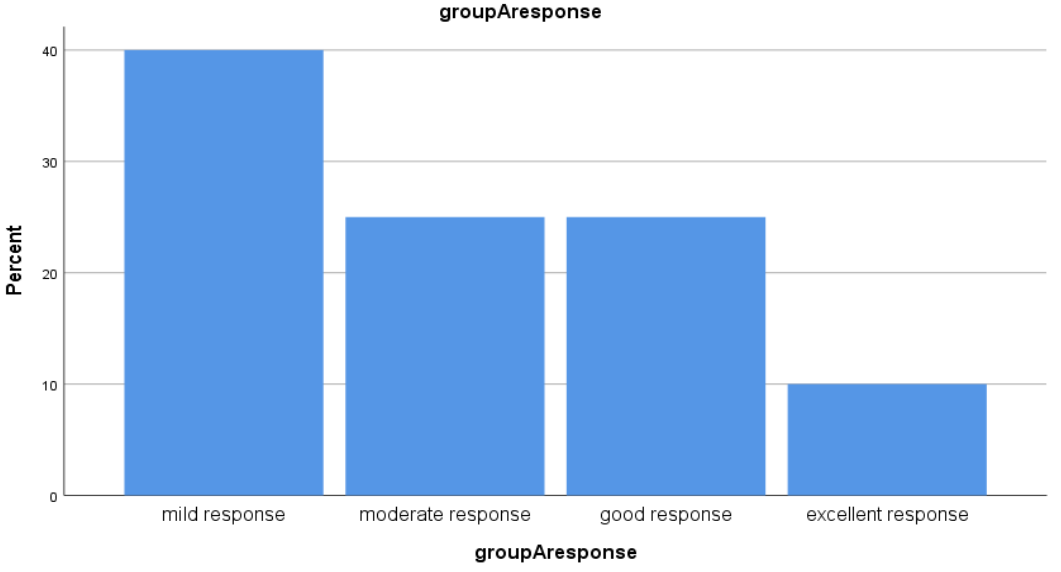
Side effect	Triamcinolone group n=20	Pentoxifyllin group n=20
Telangiectasia	5%(1)	0
Triamcinolone acetonide precipitations	0	0
Atrophy	9	0
Hypopigmentation	15%(3)	0
striae	20%(4)	0
No	60%(12)	100%(20)

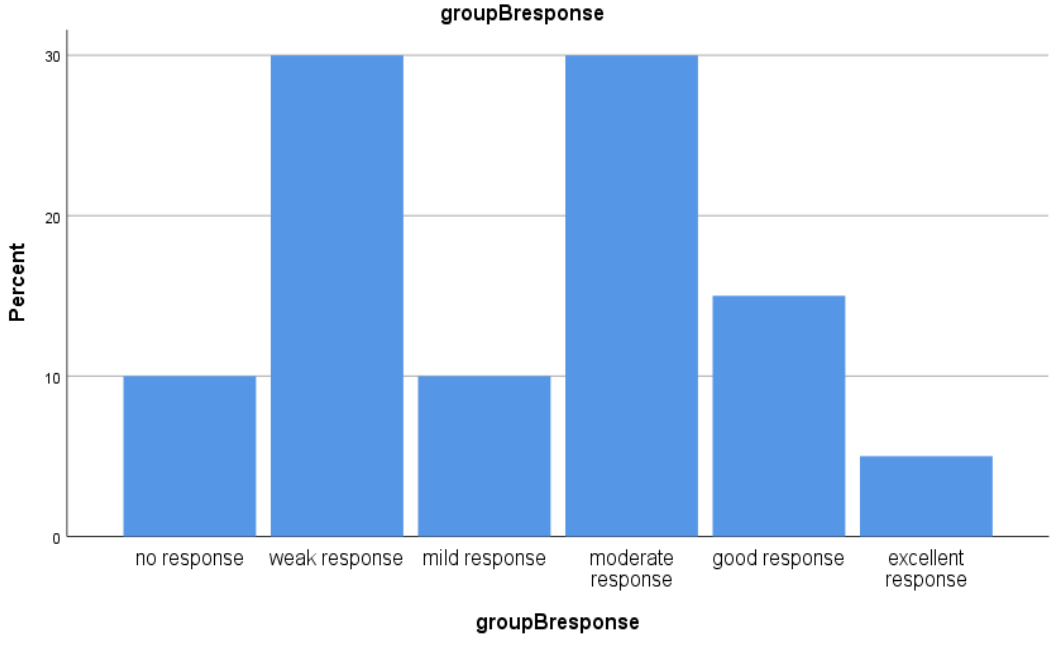
Discussion

Keloid scars is a common issue with healing of wounds. The genesis of keloid scars lesions are complicated and poorly understood. Because of the repeated inadequacies, continues to perplex both patients and clinicians. response, notable adverse effects, and the natural recurrence of the situation Recent keloid management trends encourage the use of combination therapy over monotherapy. (Lee YI et al.,2019). Even though keloid management is rather prevalent, there is still a lack of consensus(Limandjaja GC et al.,2020). The optimum treatment techniques for keloid and the effect of various combinations of keloid treatments are still being evaluated in keloid research. Intralesional triamcinolone acetonide is first-line therapy for keloid scar treatment. The TAC dosage The dose range for intralesional keloid injection has been 10 to 40 mg/ml., and the medication is administered every three to six weeks. (Mustoe TA et al.,2002) Peyronie's disease (Smith JF et al.,2011), radiation fibrosis(Fischer M et al.,2001), cystic fibrosis (Aronoff SC et al.,1994), radiation pneumonitis (Kaya V et al.,2014), oral submucous fibrosis (Liu J et al., 2018)and postburn hypertrophic scars (Isaac C., et al 2010). are only a few of the inflammatory and fibrotic disorders for which PTX has been utilized in humans. Human cultured fibroblasts from keloid, scleroderma, and morphea were found to be less proliferative and produce less collagen, glycosaminoglycans, and fibronectin when treated with pentoxifylline. (Br J Dermatol,1990).In our study among 40 patients, there was 70% were female, and 30%male the range of age is between 6-60 years old.in our study there were significant improvements in the visual analog scale in group A and group B with a p-value equal to 0.003 and 0.026 respectively(p-value <0.05) These results could be attributed to intralesional TAC's inhibitory effect on fibroblast proliferation and VEGF production, which causes scar tissue atrophy.

(Hosseini Fet al .,2019). PTX inhibits fibroblast growth and reduces the production of fibronectin, type I and III collagen, and glycosaminoglycan, all of which have anti-fibrotic properties and increase the activity of collagenase enzyme. (Tan A et al.,2020).

The greatest improvement was seen in group A patients, a decrease in height was detected in both groups and a statistically significant improvement was seen with the surface of the keloid with grouping A only. patients in group A are satisfied more than in group B. there was a statistically significant improvement in itching and pain in both groups A&B because of the inflammatory effect of both triamcinolone acetonide& pentoxifylline. pentoxifylline reduced pain and increased oxygenated blood circulation to the tissues. (Hosseini Fet al .,2019)The side effects detected in group A such as Telangiectasia, hypopigmentation, and striae, and No adverse effects were detected in group B except pain suffered during injection. This is consistent with Mikhael's discoveries. (Mikhael NW et al.,2015). the total number of sessions required for best outcomes is equal with both groups (3-6 sessions).





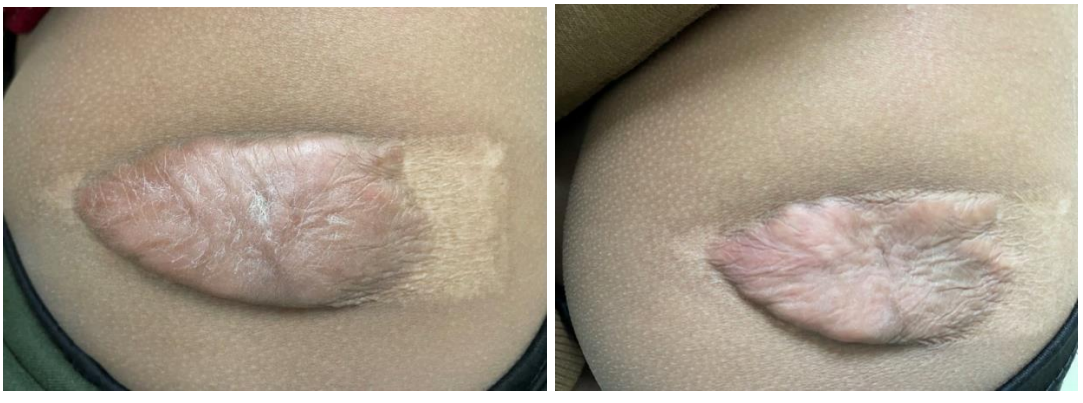


Figure 1 male patient 12 years old had keloid in the back the cause is by burn with the one-year duration the thickness before intralesional triamcinolone acetonide is 10mm with firm consistency after the treatment the thickness is 5 mm with supple consistency the number of sessions for injection is 5 every 2 weak.

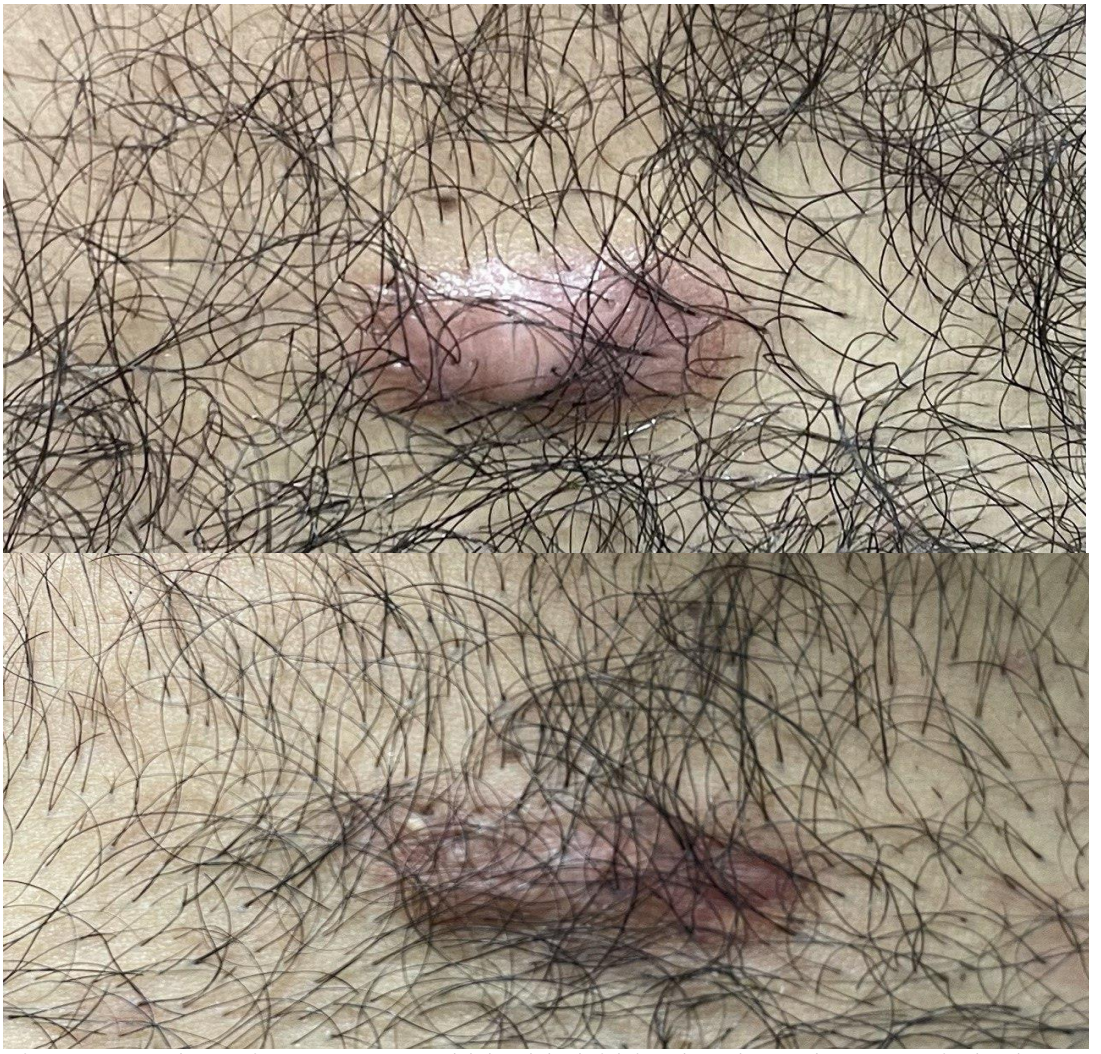


Figure 2 male patient 28 years old had keloid in the chest the cause is by burn with the one-year duration the thickness before intralesional triamcinolone acetonide is 3mm with firm consistency after the treatment the thickness is 1 mm with yeilding consistency the number of session for injection is 3 every 2 weak.

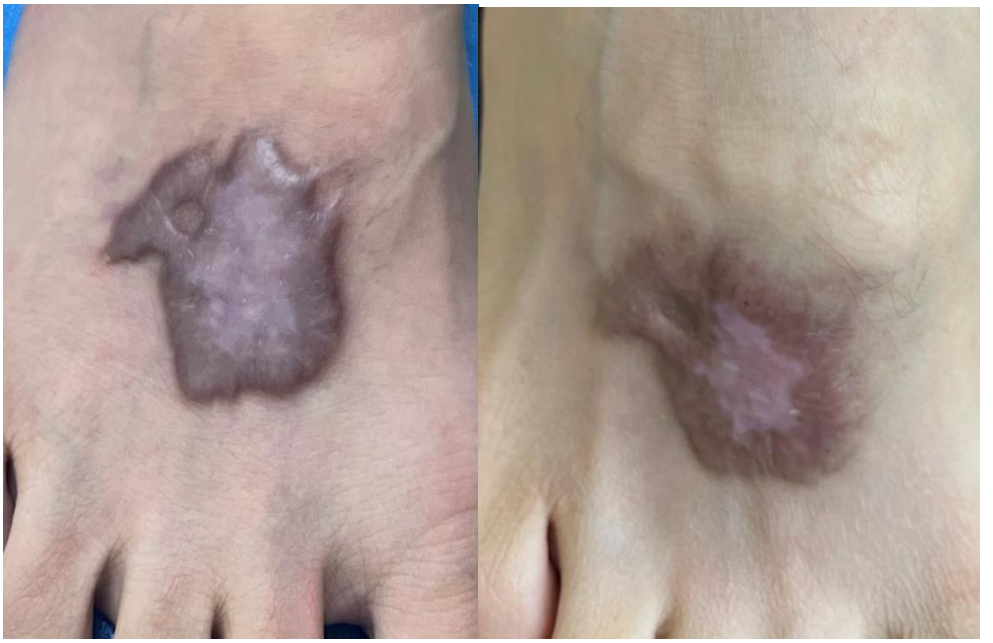


Figure 3 female patient 29 years old had keloid in the feet the cause is by burn with the 4-month duration the thickness before intralesional triamcinolone acetonide is 3mm with firm consistency after the treatment the thickness is 1 mm with firm consistency the number of sessions for injection is 6 every 2 weak.

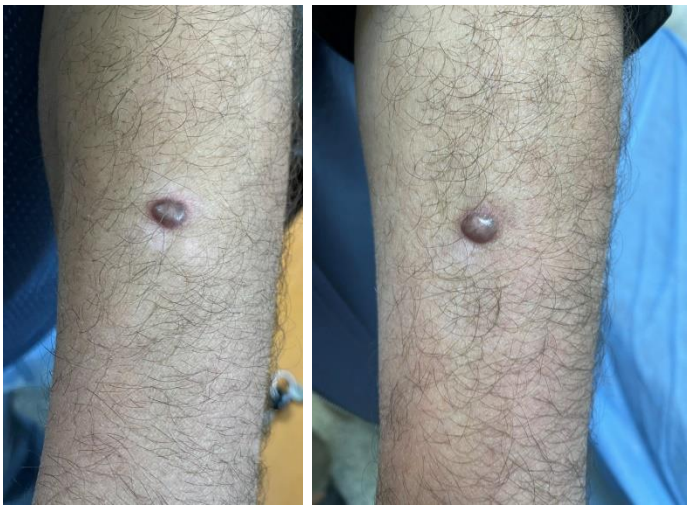


Figure 4 male patient 58 years old had a keloid in upper limp the caused by a burn with no improvement in keloid thickness after intralesional injection of pentoxifylline for sex sessions.

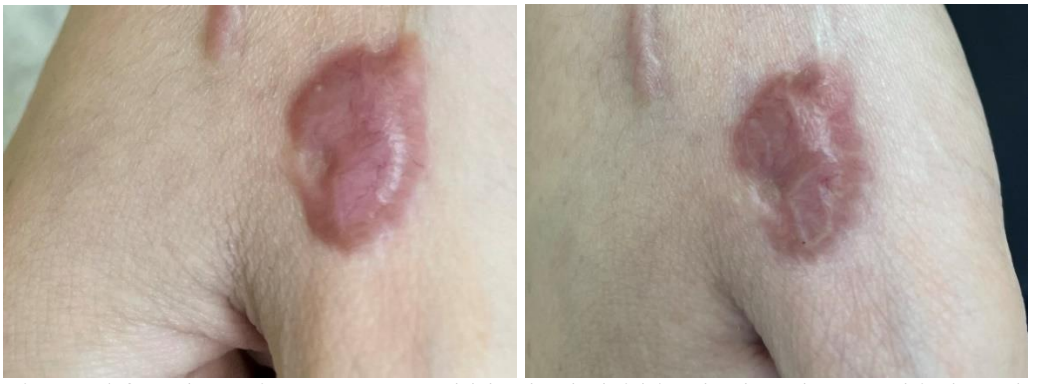


Figure 5 female patient 29 years old had a keloid in the hand caused is by a burn with a 4-month duration the thickness before intralesional pentoxifylline is 3mm with supple consistency after the treatment the thickness is 1 mm with supple consistency the number of sessions for injection is 6 every 2 weak.

Study limitations

The study's most significant weaknesses are because of the limited sample size, brief follow-up, and unavailability of studies on the use of intralesional pentoxifylline in keloid scars. The most important study limitation about the patients not complying with the treatment sessions appointments and the patient's fear of the injection.

4-Conclusion

To verify our findings and establish whether intralesional injection of pentoxifylline, either alone or in combination with other commonly employed treatments, can assist with keloid treatment or keloid scar prevention, There is a need for larger trials with larger sample sizes and longer follow-up times. Keloid scars are a widespread problem that has yet to be treated. When used alone, intralesional pentoxifylline is well-tolerated, effective and safe method of treating keloid scars, however, It is less effective than intralesional TAC. Combining pentoxifylline and triamcinolone acetonide produces better outcomes and lowers the possibility of triamcinolone acetonide related adverse affects. Their combination is safe, economical, and advised for producing a keloid that is aesthetically acceptable with fewer injection treatments.

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