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Safety and efficacy of intralesional injection of enalapril versus triamcinolone acetonide in the treatment of keloids

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Abstract

Introduction: Keloids are pathologic conditions characterized by fibroblast hyper-proliferation and excess collagen deposition. Enalapril, one of the angiotensin-converting enzyme inhibitors, has recently been highlighted as a new therapeutic modality in treating keloids. This study evaluates the effectiveness of intralesional injection of enalapril versus triamcinolone acetonide (TAA) in keloids.

Methods: Forty patients with multiple keloids were enrolled in our study. Enalapril and TAA were injected intralesionally in one session per month for three sessions. The clinical outcomes were assessed via the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS).

Results: In both groups, according to VSS and POSAS, there was a high statistically significant difference (p-value ≤ 0.01) before treatment, at the end of each session, and 3 months after treatment. There was no significant difference between both groups regarding degree of improvement. Patients treated with TAA developed more significant complications than those in the enalapril group (p-value < 0.05).

Conclusions: Both enalapril and TAA had the same clinical effect. Enalapril could be a safe alternative to steroids in the treatment of keloid and hypertrophic scars. Further studies on enalapril are needed on a large sample of patients with further focus on the mechanism of this innovative drug.

Keywords: keloid, enalapril, triamcinolone acetonide

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Introduction

Keloids are fibroproliferative dermal tumors with excessive extracellular matrix component accumulation, particularly collagen, caused by excessive expression of growth factors and inflammatory cytokines (1, 2).

The pathogenesis of both keloid and hypertrophic scars involves a hyperproliferative state due to cellular driving pathways such as transforming growth factor (TGF), vascular endothelial growth factor, and the inactivation of genes of proapoptosis (3).

The management of keloids and hypertrophic scars is clinically challenging and includes surgical excision, laser therapy, radiotherapy intralesional chemotherapeutic injection, cryotherapy, topical silicone, systemic chemotherapy, and pressure therapy. Unfortunately, none of these options provide a satisfying therapeutic outcome (4).

Steroid injection is the current first-line therapy because it breaks collagen fiber bonds in addition to having powerful anti-inflammatory properties, which helps reduce swelling, redness, tenderness, and itching. Approximately 50% of keloids are steroid-resistant and have side effects such as telangiectasia and atrophy, and so new emerging therapeutic modalities have been indicated (5).

Enalapril, an antihypertensive drug that acts as an angiotensin-converting enzyme (ACE) inhibitor, prevents angiotensin II from producing vasoconstriction, thus lowering blood pressure (6). ACE inhibitors play an important regulatory role in wound healing and the production of collagen. Enalapril also produces down-regulatory effects on type III collagen production (7).

The ACE receptors (angiotensin I and II) are strongly expressed in both human (8) and animal (9) wounded skin. The highest expression of these receptors has been detected in scars (10). The higher angiotensin type II concentration that was detected in biopsies from keloid tissues acts on angiotensin I receptors, leading to keratinocyte and fibroblast migration via shedding of heparin-binding epidermal growth factor–like growth factor, epidermal growth factor receptor transactivation, and an increase in collagen synthesis. An animal study on rats (11) concluded that activation of the receptor of angiotensin II type 1 leads to re-epithelization and recovery of myofibroblasts. However, valsartan (an angiotensin I antagonist) reduced this effect by decreasing the gene expression of collagen type 1, contractile activity, TGF-β, and monocyte chemoattractant protein-1 with a consequent reduction in the activity of myofibroblasts and trafficking monocyte to the scar tissue (12). Both topical and oral enalapril in keloids and hypertrophic scar treatment showed some efficacy with no side effects (13).

Methods

Study design

This was a prospective randomized comparative study that enrolled 40 patients with multiple keloids from December 2019 to July 2020.

We studied the effect of intralesional injection of enalapril in keloids and compared it with the effect of intralesional triamcinolone acetonide (TAA). All patients with multiple keloids in the

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selected age group (21–40 years old) were enrolled in the study. Patients with hypotension, known hypersensitivity to ACE inhibitors, pregnancy, lactation, or renal impairment were excluded.

An Arabic informed consent form was signed by every participant or a parent in the presence of one of the authors. A code number was used for every patient for data privacy and confidentiality. Photos were taken for the affected lesion only and were presented only for research purposes. Patients were instructed to report any complications: pain, erythema, ulceration, burning sensation, secondary infection, post-inflammatory hyperpigmentation, or any allergic manifestations.

This study was carried out by the Dermatology Department, Faculty of Medicine, Fayoum University. Written consent was obtained from all patients before treatment after explaining the nature, risk, and purpose of the study. All collected data were kept confidential. The study was conducted after approval from the ethics committee of the Faculty of Medicine, Fayoum University, IRB 00003613.

Procedure

Forty patients with multiple keloids were selected to participate in this study. One lesion was treated with enalapril (designated E) and another lesion on the same patient was treated with TAA (designated T). The lesion was cleansed with an appropriate cleanser. Local antiseptic was applied to minimize contamination. In group one, lesions designated E were treated with an enalapril intralesional injection at a concentration of 0.125 mg/ml using 30 units of solution during three sessions 1 month apart. The injection was made in each point of scar area with 1 cm spacing with a maximum of 2 ml of enalapril at each session using a 1 ml insulin-grade syringe. In group 2, lesions designated T in the same patients were treated with a TAA intralesional injection at a 1:1 dilution with mepivacaine during three sessions 1 month apart. Ten units of solution were injected in each point of the lesion area with 1 cm spacing with a maximum of 2 ml of TAA using a 1 ml insulin-grade syringe.

Evaluation and follow-up

The patients were examined by two experienced dermatologists before and 3 months after the last treatment using the Vancouver Scar Scale (VSS) (14) and the Patient and Observer Scar Assessment Scale (POSAS) (15). Both scores were measured at the baseline, after each session, and 3 months after the last session (final follow-up). The scores were summed each time for areas injected with TAA and enalapril.

Results

The age of our patients was between 21 and 40 years old with a mean age of 30.10 ± 9.13. Twenty-eight (70.0%) patients were females and 12 (30.0%) patients were males (Table 1). Most of the lesions were caused by scald burns (67.5% of the lesions). Other causes included trauma, inflammation, and spontaneous causes, corresponding to 22.5%, 7.5%, and 2.5% of the lesions, respectively (Fig. 1).

Regarding the site of the lesions, most of the lesions were on the upper limbs (57.5% of the lesions). Other sites included the chest, abdomen, head and neck, lower limbs, and back, corresponding to 17.5%, 12.5%, 12.5%, and 5.0% of the lesions, respectively (Fig. 2). Regarding symptoms (adverse effects), 35% of patients had no symptoms, 29% of patients complained of pain, 30% complained of itching, and 6% complained of tenderness (Fig. 3).

In both groups, according to VSS and POSAS, there was a high statistically significant difference (p-value ≤ 0.01) before treatment, at the end of each session, and 3 months after treatment (Tables 2 and 3). Table 4 shows that there was no significant difference between both groups with regard to the degree of improvement. Patients treated with TAA developed significant complications more than the enalapril group (p-value < 0.05; Table 5).

Figures 4, 5, and 6 present photos for both groups before, during, and immediately after treatment, and 3 months after treatment. Different degrees of improvement were observed.

Table 1 | Demographic data of the patients studied (n = 40).

Variable	Value
Age (years)	
Mean ± *SD*	31.10 ± 9.13
Median	35
Sex	
Male, *n* (%)	12 (30.0)
Female, *n* (%)	28 (70.0)
Male:female ratio	1: 2.3

SD = standard deviation.

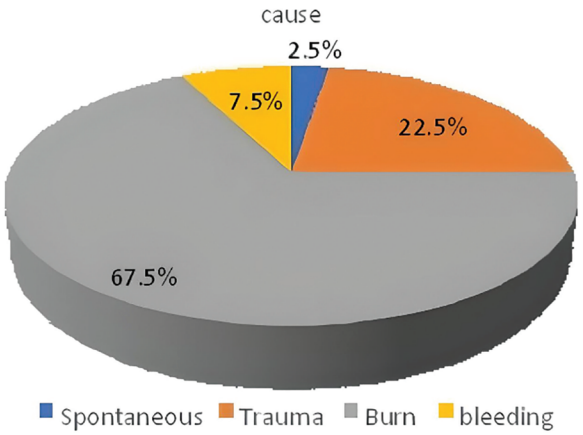

Figure 1 | Causes of keloid lesions in the study population.

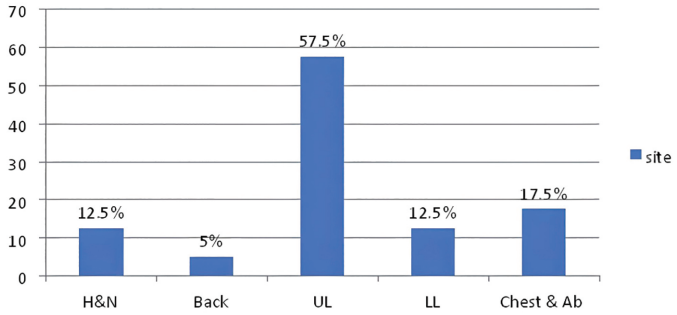

Figure 2 | Sites of keloid lesions in the patients studied.
H&N = head and neck, UL = upper limbs, LL = lower limbs, Chest&Ab = chest and abdomen.

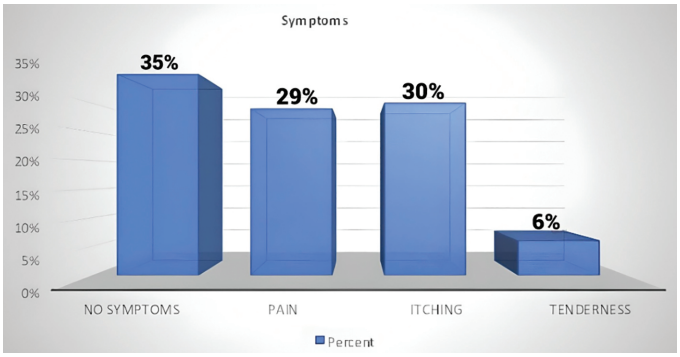

Figure 3 | Symptoms of keloid lesions in the study population.

Table 2 | **Comparison over time for lesions treated with enalapril.**

Scale: measures	Paired differences		*t*	*p*-value	Sig.
	Mean	*SD*			
Vancouver: baseline, 3 months	7.813	2.191	20.167	0.000	HS
Vancouver: baseline, follow-up	7.730	2.156	21.811	0.000	HS
Observer: baseline, 3 months	24.781	5.807	24.139	0.000	HS
Observer: baseline, follow-up	25.838	5.454	28.814	0.000	HS
Patient: baseline, 3 months	25.500	5.657	25.500	0.000	HS
Patient: baseline, follow-up	26.378	5.499	29.177	0.000	HS

Sig. = significance, HS = highly significant, *SD* = standard deviation.

Table 3 | **Comparison over time within lesions treated with triamcinolone acetonide.**

Scale: measures	Paired differences		*t*	*p*-value	Sig.
	Mean	*SD*			
Vancouver: baseline, 3 months	7.563	2.285	18.721	0.000	HS
Vancouver: baseline, follow-up	7.703	2.080	22.527	0.000	HS
Observer: baseline, 3 months	23.813	5.095	26.436	0.000	HS
Observer: baseline, follow-up	25.162	4.986	30.696	0.000	HS
Patient: baseline, 3 months	24.875	4.950	28.429	0.000	HS
Patient: baseline, follow-up	25.811	4.988	31.476	0.000	HS

Sig. = significance, HS = highly significant, *SD* = standard deviation.

Table 4 | **Comparison between the Vancouver Scar Scale and the Patient and Observer Scar Assessment Scale scores in both groups.**

Scale: measure, T vs. E	Paired differences		*t*	*p*-value	Sig.
	Mean	*SD*			
Vancouver: baseline	−0.075	0.267	−1.778	0.083	NS
Vancouver: 3 months	0.156	1.609	0.549	0.587	NS
Vancouver: follow-up	−0.054	1.779	−0.185	0.854	NS
Observer: baseline	−0.050	0.389	−0.813	0.421	NS
Observer: 3 months	0.906	3.586	1.429	0.163	NS
Observer: follow-up	0.622	3.183	1.188	0.240	NS
Patient: baseline	0.125	0.966	0.819	0.418	NS
Patient: 3 months	0.781	2.511	1.760	0.088	NS
Patient: follow-up	0.703	2.259	1.892	0.067	NS

T = triamcinolone acetonide, E = enalapril, Sig. = significance, NS = not significant, *SD* = standard deviation.

Table 5 | **Comparison between complications after 3 months in both groups.**

	Complications, E			
	None	Tingling	Scaling	Total
None				
n	26	1	0	27
% within complications, T	96.3	3.7	0.0	100.0
% within complications, E	86.7	100.0	0.0	84.4
% of total	81.3	3.1	0.0	84.4
Hypopigmentation				
n	4	0	0	4
% within complications, T	100.0	0.0	0.0	100.0
% within complications, E	13.3	0.0	0.0	12.5
% of total	12.5	0.0	0.0	12.5
Scaling				
n	0	0	1	1
% within complications, T	0.0	0.0	100.0	100.0
% within complications, E	0.0	0.0	100.0	3.1
% of total	0.0	0.0	3.1	3.1
Total				
n	30	1	1	32
% within complications, T	93.8	3.1	3.1	100.0
% within complications, E	100.0	100.0	100.0	100.0
% of total	93.8	3.1	3.1	100.0

E = enalapril, T = triamcinolone acetonide.

Discussion

No single treatment modality proves universally optimal for addressing all keloid cases. Many therapeutic modalities have been used to treat keloids and reduce recurrence. Surgical excision and superficial radiation therapy is the most effective modality (16). Other modalities include occlusive dressings, compression therapy, cryosurgery, intralesional corticosteroid injections, radiation therapy, excision, interferon therapy, laser therapy, 5-fluorouracil, bleomycin, doxorubicin, verapamil, imiquimod 5% cream, retinoic acid, tacrolimus, tamoxifen hydrogel scaffold, botulinum toxin, and over-the-counter treatments.

Our study evaluated two treatment modalities in treating keloids, seeking promising results with fewer side effects. We studied the effect of intralesional injection of enalapril in keloids and compared it with the effect of intralesional TAA to establish its possible role in treating this common and bothersome condition.

This study was conducted on 40 patients with multiple keloids. In the same patient, we used one lesion for enalapril injection and the other for TAA injection.

The findings indicate that younger patients, owing to their higher levels of physical activity, are more susceptible to trauma, rendering them more prone to keloid formation (17). We selected the patients we studied from a younger age group (between 21 and 40 years old with a mean age of 30.10 ± 9.13). Because females seek medical advice more than males due to cosmetic concerns (18), most of the patients studied were females 28 (70%).

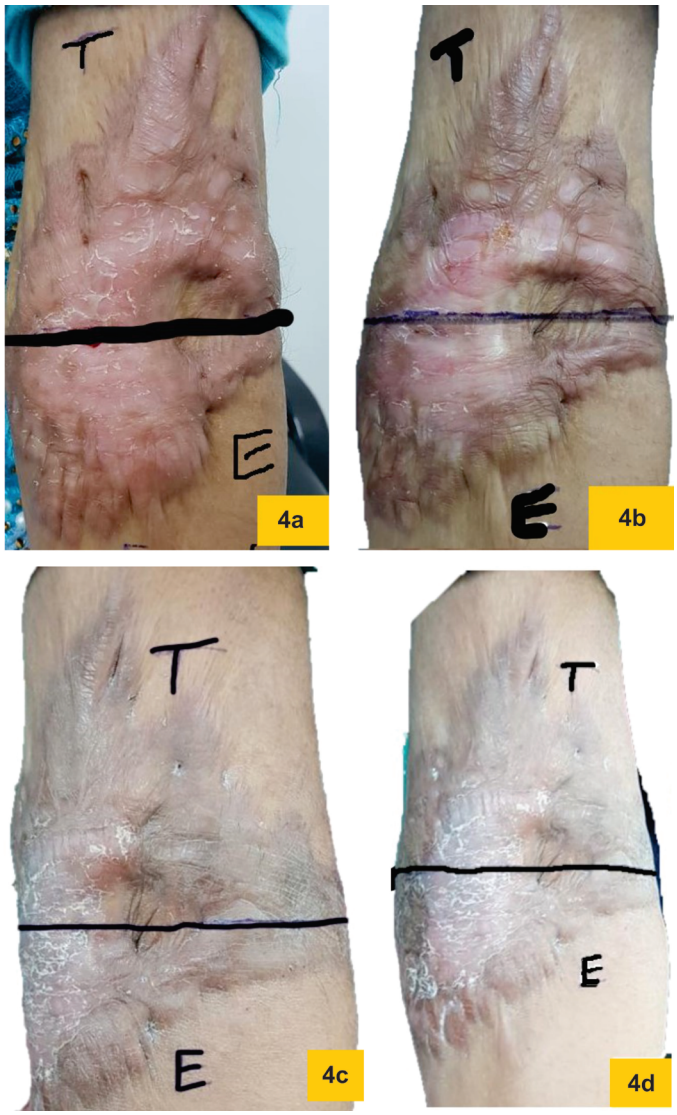

Figure 4 | A) prior to treatment, B) during treatment, C) immediately following treatment, D) three months post-treatment (mild improvement).

Most of the lesions in the patients studied were caused by scald burns (67.5% of the lesions). Other causes of the lesions included trauma, inflammation, and spontaneous causes, corresponding to 22.5%, 7.5%, and 2.5% of the lesions, respectively. Burns repre-

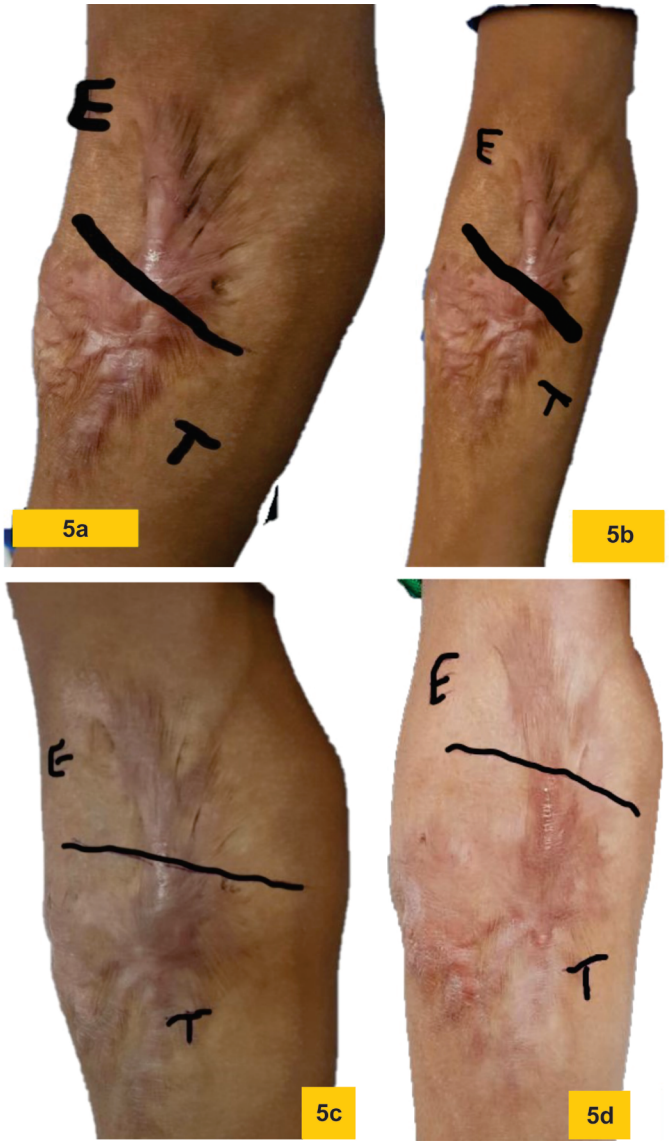

Figure 5 | A) prior to treatment, B) during treatment, C) immediately following treatment, D) three months post-treatment (moderate improvement).

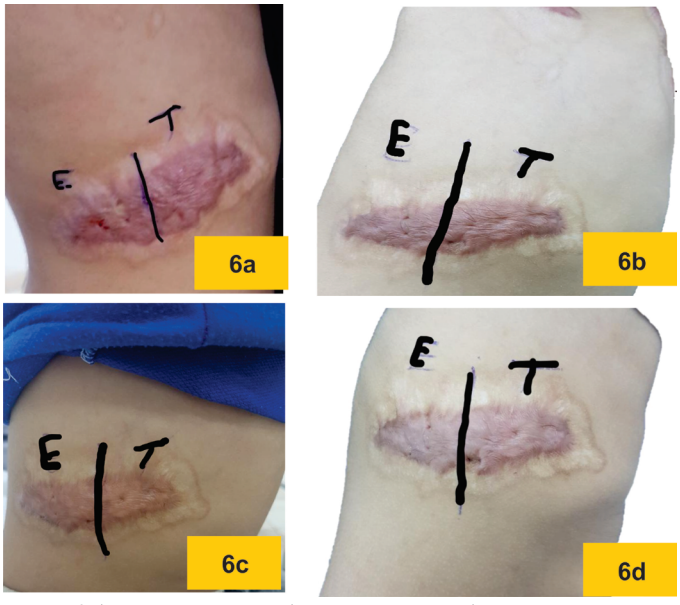

Figure 6 | A) prior to treatment, B) during treatment, C) immediately following treatment, D) three months post-treatment (marked improvement).

sent the major cause of such scars due to the lack of safety measures in Egypt.

In this study, most lesions were found on the upper limbs. This group accounted for 57.5% of the lesions. The upper limbs are more exposed to various trauma and thus keloid and hypertrophic scars.

Among our patients, 35% had no symptoms related to the scar. However, 29%, 30%, and 6% of our patients complained of pain, itching, and tenderness, respectively.

In both groups, significant improvements (before and immediately after treatment, and at the final follow-up 3 months after treatment) were found in the treatment of keloids based on clinical assessment by the VSS and the POSAS, with a p-value ≤ 0.01. Our study also showed that the greatest improvement was detected after the first and second sessions, but the third session did not add much difference. The greatest improvement on the VSS was seen after the second session. This could be an encouragement to use only two sessions in future work.

We used intralesional injection of enalapril based on its capability to decrease collagen deposition, as well as its remodeling and antifibrotic effects (19).

Alexandrescu et al. (3) published a case report that included only one patient with multiple keloids treated with various modalities, including enalapril. The study revealed that intralesional enalapril led to the resolution of itching and pain.

Moreover, Mohammadi et al. used topical enalapril (20), and Ogawa et al. (21) used oral captopril; both studies reported significant improvement.

Although a significant proportion of the enalapril group developed complications— tingling in two (5%) patients, local bleeding in two (5%), and pain in four (10%)—the reported complications were self-limited and very mild in severity compared to the group treated with TAA (p-value ≤ 0.01). The TAA-treated group reported more frequent and severe complications after each session of injection and between baseline and 3 months after the third session (final follow-up).

This was in line with the findings of Khalid et al. (22) and Hietanen et al. (5), who documented that intralesional TAA injection lowered the scar elevation index significantly when used with keloids. Similarly, several studies (5, 20, 23–26) found that the most common adverse side effects of corticosteroid injection were hypopigmentation, pain, and atrophy.

In our study, no statistically significant difference was found with a p-value ≥ 0.05 between the baseline scores of both groups, results of both group scores after the third session, and the results of both group scores at the final follow-up session.

Many strengths can be clearly identified in our study: 1) to the best of our knowledge, it is the first study to evaluate the role of intralesional enalapril in the treatment of keloids; 2) it studied an adequate number of patients; 3) it was a prospective and controlled study; and 4) the study population included both sexes. In addition, two validated clinical assessment scores were used.

Limitations of our study include a lack of pathologic correlation and the fact that other concentrations of enalapril were not tried. This could be done in further studies.

In conclusion, our study revealed that enalapril has almost the same clinical effects on keloids as triamcinolone acetonide, but with significantly fewer complications. Further studies on enalapril in the treatment of keloid scars are needed on a large sample

of patients with further focus on its mechanism of action and its molecular effect by taking biopsies before and after treatment.

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References

1. Rabello FB, Souza CD, Farina Júnior JA. Update on hypertrophic scar treatment. Clinics (Sao Paulo). 2014;69:565–73.
2. Andrews JP, Marttala J, Macarak E, Rosenbloom J, Uitto J. Keloids: the paradigm of skin fibrosis—pathomechanisms and treatment. Matrix Biol. 2016;51:37–46.
3. Alexandrescu D, Fabi S, Yeh LC, Fitzpatrick RE, Goldman MP. Comparative results in treatment of keloids with intralesional 5-FU/Kenalog, 5-FU/verapamil, enalapril alone, verapamil alone, and laser: a case report and review of the literature. J Drugs Dermatol. 2016;15:1442–7.
4. Jones CD, Guiot L, Samy M, Gorman M, Tehrani H. The use of chemotherapeutics for the treatment of keloid scars. Dermatol Reports. 2015;7:5880.
5. 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.
6. Bratsos S. Efficacy of angiotensin converting enzyme inhibitors and angiotensin receptor-neprilysin inhibitors in the treatment of chronic heart failure: a review of landmark trials. Cureus. 2019;11:e3913.
7. Uzun H, Bitik O, Hekimoğlu R, Atilla P, Kaykçoğlu AU. Angiotensin-converting enzyme inhibitor enalapril reduces formation of hypertrophic scars in a rabbit ear wounding model. Plast Reconstr Surg. 2013;132:361e–71e.
8. Steckelings UM, Henz BM, Wiehstutz S, Unger T, Artuc M. Differential expression of angiotensin receptors in human cutaneous wound healing. Br J Dermatol. 2005;153:887–93.
9. Hedayatyanfard K, Haddadi NS, Ziai SA, Karim H, Niazi F, Steckelings UM, et al. The renin–angiotensin system in cutaneous hypertrophic scar and keloid formation. Exp Dermatol. 2020;29:902–9.
10. Morihara K, Takai S, Takenaka H, Sakaguchi M, Okamoto Y, Morihara T, et al. Cutaneous tissue angiotensin-converting enzyme may participate in pathologic scar formation in human skin. J Am Acad Dermatol. 2006;54:251–7.
11. Takeda H, Katagata Y, Hozumi Y, Kondo S. Effects of angiotensin II receptor signaling during skin wound healing. Am J Pathol. 2004;165:1653–62.
12. Murphy A, LeVatte T, Boudreau C, Midgen C, Gratzer P, Marshall J, et al. Angiotensin II type I receptor blockade is associated with decreased cutaneous scar formation in a rat model. Plast Reconstr Surg. 2019;144:803e–13e.
13. Huang C, Liu L, You Z, Du Y, Ogawa R. Managing keloid scars: from radiation therapy to actual and potential drug deliveries. Int Wound J. 2019;16:852–9.
14. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. J Burn Care Rehabil. 1995;16:535–8.
15. Draaijers LJ, Tempelman FR, Botman YA, Tuinebreijer WE, Middelkoop E, Kreis RW, et al. The Patient and Observer Scar Assessment Scale: a reliable and feasible tool for scar evaluation. Plast Reconstr Surg. 2014;113:1960–5.
16. Berman B, Nestor MS, Gold MH, Goldberg DJ, Weiss ET, Raymond I. A retrospective registry study evaluating the long-term efficacy and safety of superficial radiation therapy following excision of keloid scars. J Clin Aesthet Dermatol. 2020;13:12–6.
17. Michael AI, Ademola SA, Olawoye OA, Iyun AO, Adebayo W, Oluwatosin OM. Pediatric keloids: a 6-year retrospective review. Pediatr Dermatol. 2017;34:673–6.
18. Noishiki C, Hayasaka Y, Ogawa R. Sex differences in keloidogenesis: an analysis of 1659 keloid patients in Japan. Dermatol Ther (Heidelb). 2019;9:747–54.
19. Abhishek V. Effect of enalapril on hypertrophic scars and keloids. J Adv Plast Sur Res. 2015;1:10–3.
20. Mohammadi AA, Parand A, Kardeh S, Janati M, Mohammadi S. Efficacy of topical enalapril in treatment of hypertrophic scars. World J Plast Surg. 2018;7:326–31.
21. Ogawa R, Arima J, Ono S, Hyakusoku H. Case report: total management of a severe case of systemic keloids associated with high blood pressure (hypertension): clinical symptoms of keloids may be aggravated by hypertension. Eplasty. 2013;13:e25.
22. Khalid FA, Mehrose MY, Saleem M, Yousaf MA, Mujahid AM, Rehman SU, et al. Comparison of efficacy and safety of intralesional triamcinolone and combination of triamcinolone with 5-fluorouracil in the treatment of keloids and hypertrophic scars: randomised control trial. Burns. 2019;45:69–75.
23. McGinty S, Siddiqui WJ. Keloid. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507899/.
24. Morelli Coppola M, Salzillo R, Segreto F, Persichetti P. Triamcinolone acetonide intralesional injection for the treatment of keloid scars: patient selection and perspectives. Clin Cosmet Investig Dermatol. 2018;11:387–96.
25. Saki N, Mokhtari R, Nozari F. Comparing the efficacy of intralesional triamcinolone acetonide with verapamil in treatment of keloids: a randomized controlled trial. Dermatol Pract Concept. 2019;9:4–9.
26. Huu ND, Huu SN, Thi XL, Van TN, Minh PPT, Minh TT, et al. Successful treatment of intralesional triamcilonon acetonide injection in keloid patients. Open Access Maced J Med Sci. 2019;7:275–8.