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EFFICACY OF INTRALESIONAL VERAPAMIL HYDROCHLORIDE VERSUS INTRALESIONAL TRIAMCINOLONE ACETONIDE IN HYPERTROPHIC SCARS AND KELOIDS

By

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ABSTRACT

Background: Keloids and hypertrophic scars are dermal fibro-proliferative disorders lead to disfigurement, pain and pruritus. Their management is still challenging as there is no universally accepted treatment regimen. Corticosteroid injections, most commonly triamcinolone acetonide, continue to play a major role in the management of keloids. Verapamil is a phenylalkylamine calcium channel blocker antiarrhythmic agent that has antifibrotic effect.

Objective: To compare efficacy of intralesional verapamil hydrochloride and triamcinolone acetonide in hypertrophic scars and keloids.

Patients and methods: Forty Egyptian patients with keloids or hypertrophic scars were divided into two equal groups. The patients were recruited from the Dermatology outpatient clinics of Al-Zahraa University Hospital during the period from May 2016 to May 2017. Informed written consents were obtained from all patients.

Group A: Intralesional Verapamil Hydrochloride.

Group B: Intralesional Triamcinolone Acetonide.

The efficacy of treatment was evaluated by Digital photography and Vancouver scar scale before and after treatment. Two- fine millimeter punch biopsies were taken from 5 patients of the verapamil group before and after treatment to demonstrate the histopathological changes induced by verapamil.

Results: Both drugs improved total Vancouver scar scale, vascularity score and pliability score of keloid or hypertrophic scar nearly equally with no statistical significant difference. Both drugs improved height of keloid or hypertrophic scar significantly, but triamcinolone showed better improvement. Verapamil highly improved pigmentation score of keloids and hypertrophic scars, but triamcinolone showed non- significant improvement. Side effects were reported in 4 patients of triamcinolone group with no side effects in verapamil group.

The histopathological examination after treatment with verapamil injection showed marked reduction of collagen deposition and alteration of the fibroblast shape (from elongated to spherical), and these changes are similar to histopathological changes which occur after corticosteroids injection.

Conclusion: Verapamil was among the several therapeutic modalities, have an option for keloids and hypertrophic scars with an extremely low cost and fewer adverse effects.

Keywords: Keloids, Hypertrophic scars, Verapamil, Triamcinolone.

INTRODUCTION

Keloids and hypertrophic scars are dermal fibro-proliferative disorders unique to human *(Lorenz and Bari, 2012)*, which may lead to intermittent pain, persistent itching, and a sensation of contraction. Moreover, if the wounds are located on the joints or mobile regions, including the neck, the resulting scars can develop into scar contractures *(Ogawa, 2017)*.

Their management is still challenging as there is no universally accepted treatment regimen *(Berman et al., 2017)*.

Most therapeutic options ranging from surgical to non-surgical methods have potential effectiveness as both monotherapy and as combination therapy for the management of abnormal scarring. In some cases, surgical approaches are inadvisable, and in such cases, intralesional injection plays an important role in the treatment *(Viera et al., 2010)*.

Since the mid-1960s, corticosteroid injections, most commonly triamcinolone acetonide, have been a popular treatment for pathological scars, and keloids *(Gupta and Sharma, 2011)*. The function of corticosteroids is to inhibit the inflammatory cell migration and also to suppress the proliferation of fibroblasts, especially at high doses of the drug *(Perdansari et al., 2015)*.

Verapamil is a phenylalkylamine calcium channel blocker antiarrhythmic agent that can treat keloids and hypertrophic scars by increasing procollagenase synthesis, reducing extracellular matrix production, inhibiting fibroblast proliferation, as well as inhibiting the expression of IL-6, VEGF, and TGF-β1 in fibroblasts *(Yang et al., 2017)*. It also leads to depolymerization of actin filaments, cell conformational changes, apoptosis, and inhibition of fibroblast proliferation and migration *(Li and Jin, 2016)*.

The universally used scale was the Vancouver Scar Scale (VSS), which was developed by Sullivan et al. in 1990 and calculates and aggregates points in 4 categories: the vascularity, pigmentation, pliability, and height of scars *(Aggarwal et al., 2018)*. Since the publication of the Patient and Observer Scar Assessment Scale (POSAS), there have also been attempts to include subjective symptoms such as pain and urtication, which had not been considered in previous scar assessment scales. For the assessment of newly developed operative scars, the POSAS was most used. Meanwhile, for categories depending on the treatment methods for preexisting scars, the Vancouver Scar Scale (VSS) was used; the POSAS and VSS are the most frequently used scar assessment scales *(Wang et al., 2021)*.

The purpose of this study was to compare efficacy of intralesional Verapamil Hydrochloride and Triamcinolone Acetonide in Hypertrophic Scars and Keloids.

PATIENTS AND METHODS

This comparative study was conducted on 40 Egyptian patients with keloids or hypertrophic scars. The patients were recruited from the Dermatology outpatient clinics of Al-Zahraa University Hospital during the period from May 2016 to May 2017. Informed written consents were obtained from all patients. The patients were randomly divided into two equal groups **Group A** were treated by Intralesional Verapamil Hydrochloride at a concentration of 2.5mg/ml. injection every two to three weeks for a maximum of eight sessions or till complete flattening of the scar whichever came earlier, **Group B** were treated by Intralesional Triamcinolone Acetonide at a concentration of 40mg/ml. injection every two to three weeks for a maximum of eight sessions or till complete flattening of the scar whichever came earlier. No attempt was made to distinguish between hypertrophic scars and keloids. Using Vancouver scar scale before and after treatment:

1. Scar height was accurately measured with calipers.
2. Scar pliability was subjectively assessed by palpation.
3. Scar vascularity was rated on visual inspection and the rate of refill after blanching.
4. Scar pigmentation was assessed after blanching and comparing the scar color with the surrounding skin.

The decreasing value of the score indicated clinical improvement of the scar.

Two- fine millimeter punch biopsy was taken from 5 patients of the verapamil group before and after treatment under deeply infiltrated local anesthesia (xylocaine 2% without adrenaline) to demonstrate the histopathological changes induced by verapamil. Sections from each specimen were stained with Hematoxylin and Eosin (H and E) for histological study and with Trichrome (Masson stain) for better demonstration of collagen fibers and effect of verapamil on them.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

Chi-square test: it was used to compare between different groups with categorical variables.

Independent t-test: it was used to compare between two studied groups with normally quantitative variables.

Probability (P-value): P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant and P-value >0.05 was considered insignificant.

RESULTS

This comparative study included 40 keloids and hypertrophic scars patients. Group (A) Verapamil group included 16 males (80%) and 4 females (20%) and Group (B) Triamcinolone group included 14 males (70%) and 6 females (30%).

As regard age distribution in both groups, in Group (A) Verapamil group age ranged from 18 to 55 years (Mean ± SD=31.15 ± 11.54). In Group (B) Triamcinolone group age ranged from 18 to 59 years (Mean ± SD=33.50 ± 13.04) with no significant differences as regard sex and age in both groups **(Table 1)** and **(Table 2)**.

Table (1): Comparison between two groups regarding sex

Groups / Sex	Total No. (%)	Group(A) Verapamil No. (%)	Group(B) Triamcinolone No. (%)	P- value
Male	30(75.0)	16(80.0)	14(70.0)	0.465
Female	10(25.0)	4(20.0)	6(30.0)	
Total	40(100)	20(100)	20(100)	

Table (2): Comparison between two groups regarding age

Groups / Age	Group (A) Verapamil	Group (B) Triamcinolone	P-value
	No.= 20	No.= 20	
Mean ± SD	31.15 ± 11.54	33.50 ± 13.04	0.550
Range	18 – 55	18 – 59	

As regard scar location, Group (A) Verapamil group included 20 patients with different scar locations where 8(40%) of them where presternal, 6 (30%) on the extremities, 5 (25%) on the face, 1 (5%) torso- back. Group (B) Triamcinolone group included 20 patients with different scar locations where 10(50%) of them where presternal, 6 (30%) on the extremities, 1(5%) on the face, 3 (15%) torso- back, with no significant differences in both groups **(Table 3)**.

Table (3): Comparison between two groups regarding scar location.

Groups / Scar location	Total No. (%)	Group(A) Verapamil No. (%)	Group(B) Triamcinolone No. (%)	P- value
Pre-sternal	18(45.0)	8(40.0)	10(50.0)	0.525
Extremities	12(30.0)	6(30.0)	6(30.0)	1.000
Face	6(15.0)	5(25.0)	1(5.0)	0.076
Torso-back	4(10.0)	1(5.0)	3(15.0)	0.291
Total	40(100)	20(100)	20(100)	-

The height score in Group (A) ranged from 1-3mm (Mean ± SD =2.30 ± 0.57) and the height score in Group (B) ranged from 2-3mm (Mean ± SD = 2.55 ± 0.51). Comparing the improvement in height score between both groups (A and B) we found that Triamcinolone had better effect than verapamil where P value =0.008 which is highly significant so, both drugs improved height of keloid or hypertrophic scar but triamcinolone showed better improvement **(Figure 1)**.

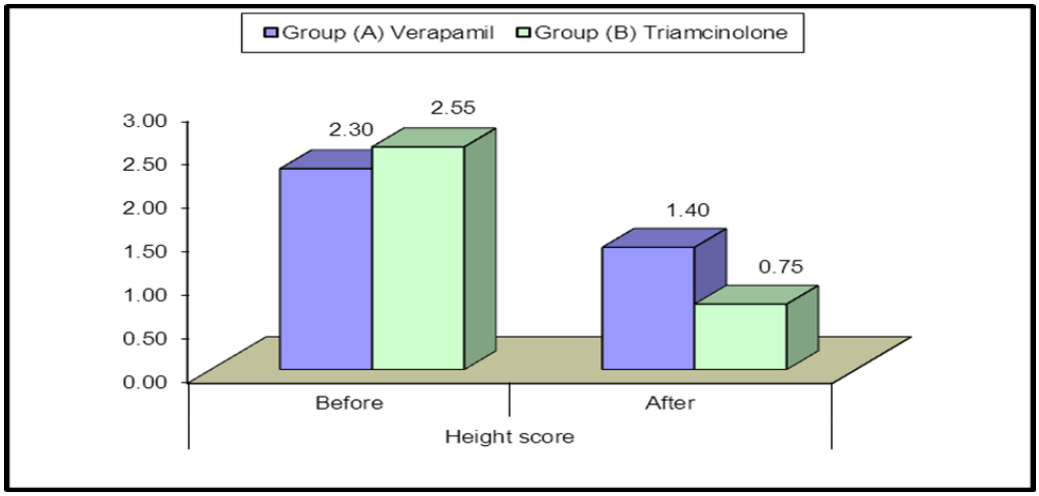

Figure (1): Comparison between group (A) and group (B) regarding Mean Height score before and after treatment. Triamcinolone is better

The vascularity score in Group (A) ranged from 0-3 (Mean ± SD =1.75 ± 0.79) and the vascularity score in Group (B) ranged from 0-3 (Mean ± SD = 1.70 ± 0.92). Comparing the improvement in vascularity score that occurred in both groups there was no statistical significant difference between both drugs where P value =0.525. So, both drugs improved vascularity of keloid or hypertrophic scar nearly equally **(Figure 2)**.

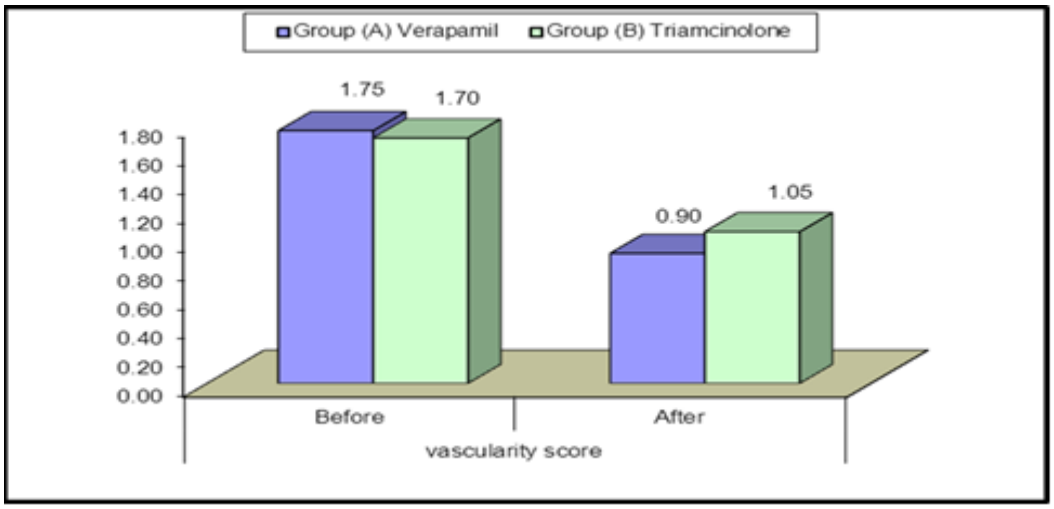

Figure (2): Comparison between group (A) and group (B) regarding Mean Vascularity score before and after treatment

The pliability score in Group (A) ranged from 1-3 (Mean ± SD =2.70± 0.57) and the pliability score in Group (B) ranged from 2-3 (Mean ± SD = 2.65 ± 0.49). Comparing the improvement in pliability score between both groups (A and B) we found that, no statistical significant difference between both drugs where P value =0.255. So, both drugs improved pliability of keloid or hypertrophic scar nearly equally **(Figure 3)**.

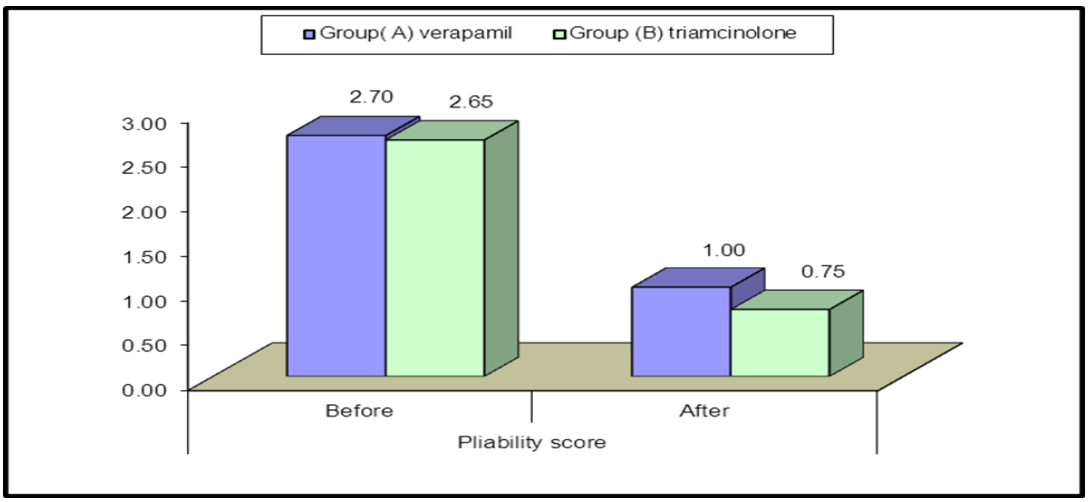

Figure (3): Comparison between group (A) and group (B) regarding Mean Pliability score before and after treatment

The pigmentation score in Group (A) ranged from 0-2 (Mean ± SD =1.70± 0.66) and the pigmentation score in Group (B) ranged from 0-2 (Mean ± SD = 1.85 ± 0.49). Comparing the improvement in pigmentation between both groups (A and B) we found that, there was statistical significant difference between both drugs where P value =0.04. So, verapamil highly improved pigmentation of keloids and hypertrophic scars but triamcinolone showed non- significant improvement **(Figure 4)**.

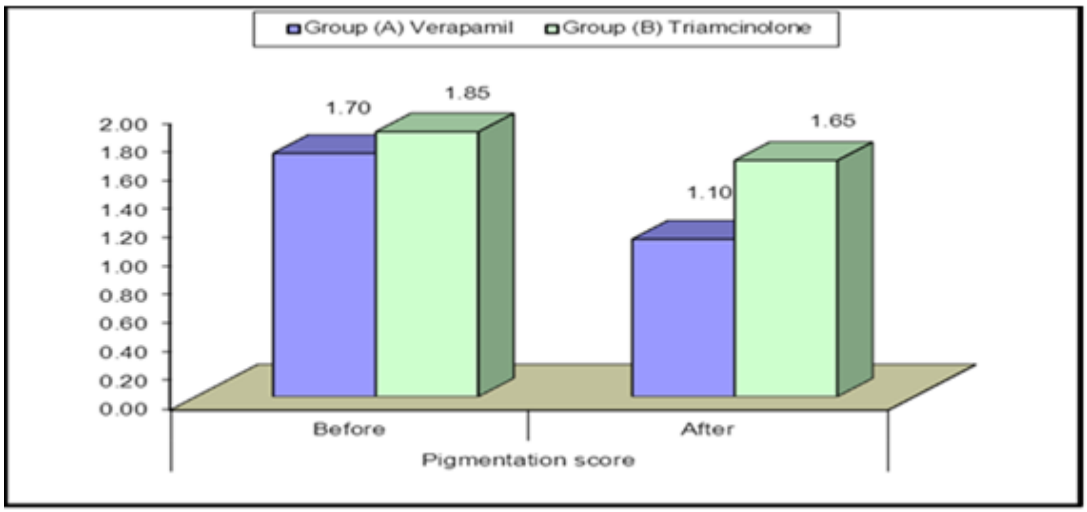

Figure (4): Comparison between group (A) and group (B) regarding Mean Pigmentation score before and after treatment

The total VSS score in Group (A) ranged from 7-11 (Mean ± SD =8.35± 1.27) and the total VSS score in Group (B) ranged from 5-11 (Mean ± SD = 8.90 ± 1.65). Comparing the improvement in the total VSS between both groups (A and B) we found that, no statistical significant difference between both drugs where P value =0.78. So, both drugs improved total VSS of keloid or hypertrophic scar nearly equally **(Figure 5)**.

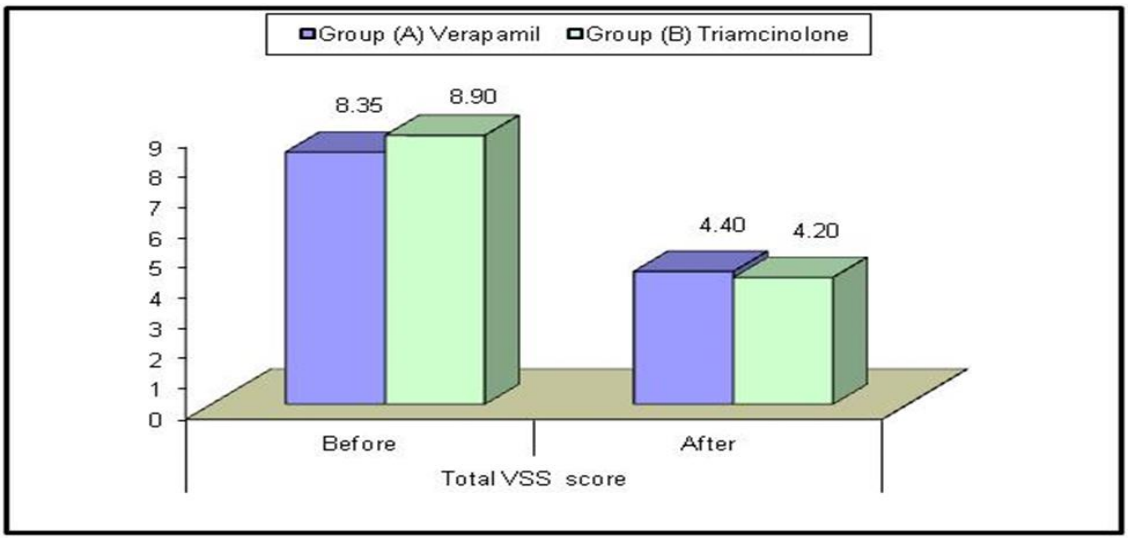

Figure (5): Comparison between group (A) and group (B) regarding total VSS before and after treatment

So, efficacy of verapamil was nearly equal to that of intralesional corticosteroid **(Figures 6 & 7)**.

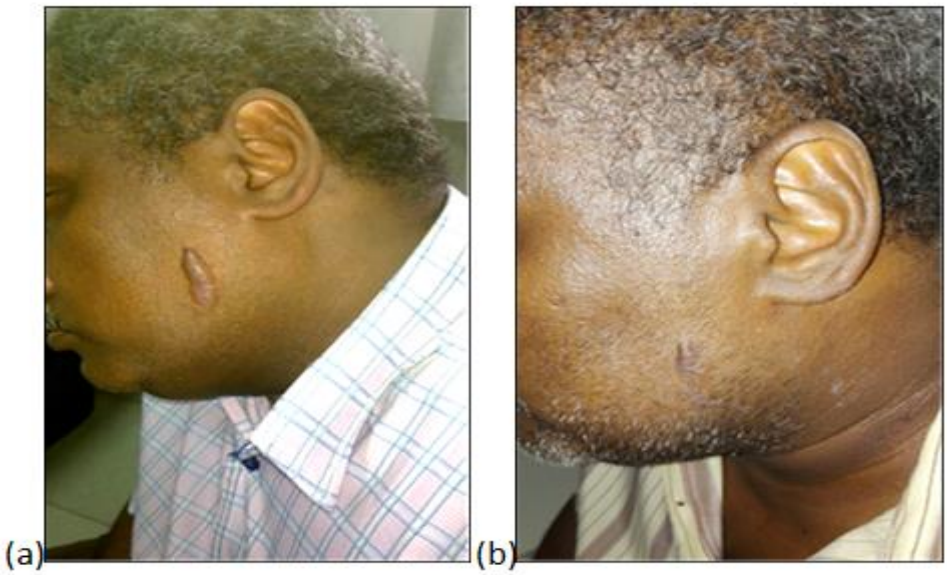

Figure (6): Facial Keloid before (a) and after treatment (b) with verapamil.VVS score improved from 8 to 3

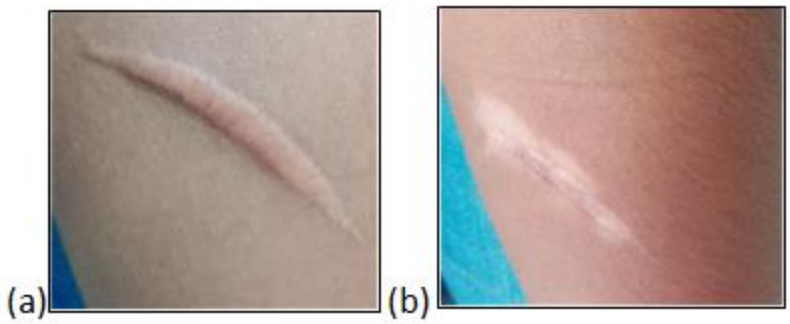

Figure (7): Facial Keloid before (a) and after treatment (b) with intralesional triamcinolone acetonide. VVS score improved to 1 after 8 sessions but led to hypopigmentation

Histopathological results showed marked reduction of collagen deposition with alteration of the fibroblast shape (from elongated to spherical) (Masson x400) **(Figure 8)**.

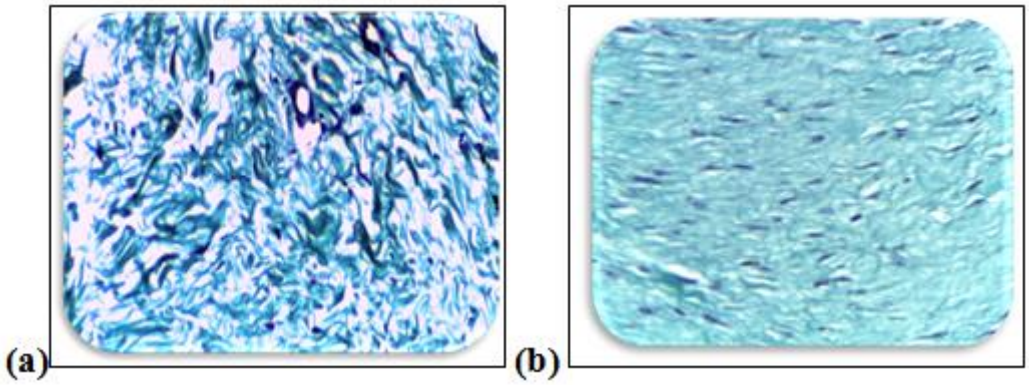

Figure (8): Histopathology of keloid before (a) and after (b) treatment with verapamil injection

DISCUSSION

Abnormal wound healing leads to the occurrence of keloids and hypertrophic scars *(Berman et al., 2017)* due to proliferation of fibroblast cells and the formation of a large extracellular matrix with excessive collagen synthesis and deposition *(Ogawa et al., 2012).*

Glucocorticoids have been recognized as the first-line drugs for keloid. They suppress the proliferation of fibroblasts of keloids and hypertrophic scars and inhibit collagen synthesis; they also increase collagenase production and reduce the level of collagenase inhibitors. Nevertheless, the side effects of glucocorticoids lead to some restrictions for their utilization; also the presence of steroid non responders hinders steroids to be effective in all patients *(Perdansari et al., 2015).*

Another important option for the treatment of keloids and hypertrophic scars include the administration of 5-fluorouracil, bleomycin, interferon and

cryotherapy and many other modalities *(Tripathi et al., 2020).*

In 1992, Lee first reported the use of the calcium channel blocker verapamil for keloid treatment and immediately attracted the attention of clinicians. Verapamil has been proven to increase the synthesis of procollagenase in keloids, hypertrophic scars, and normal cultured fibroblasts. It also leads to depolymerization of actin filaments, cell conformational changes, and apoptosis, this ultimately reduce the production of fibrous tissue *(Berman et al., 2017).* Also verapamil inhibits the synthesis of extracellular matrix molecules, including collagen, glycosaminoglycans, and fibronectin, and increases collagenase *(Boggio et al., 2011).* Increased cytokine (interleukin) IL-6 and vascular endothelial growth factor levels have been shown to be expressed in keloid fibroblasts that contribute to matrix abnormalities and cell proliferation *(Yang and Huang, 2010).* In cell cultures, verapamil has been observed to decrease IL-6 and vascular endothelial growth factor production in the central keloid fibroblasts, which lead to decrease cell proliferation, increase apoptosis and inhibition of fibroblast proliferation and migration *(Li and Jin, 2016).*

Our results showed that on comparing the improvement in the total VSS, there were no statistical significant difference between intralesional verapamil and intralesional triamcinolone acetonide and both drugs improved total VSS of keloid or hypertrophic scar nearly equally. But hypopigmentation which is considered to be the main adverse effect of Triamcinolone didn't occur with Verapamil injection.

In line with our results, a RCT conducted by Ahuja and Chatterjee found a reduction in vascularity, pliability, and height of the scars with both triamcinolone and verapamil injections but this reduction was faster by triamcinolone injection and they concluded that verapamil is almost as effective as TAC and offers several therapeutic possibilities in addition, such as use with triamcinolone in an alternating fashion or even simultaneously in the treatment of larger or multiple scars *(Ahuja and Chatterjee, 2014).*

Also, another study concluded that there was no difference in the therapeutic effect of verapamil and triamcinolone on the treatment of HSC and keloids, however, verapamil was more acceptable with fewer side effects and cost *(Zamanian et al., 2017).*

In contrast to our results, meta-analysis study concluded that triamcinolone treatment showed significantly better effectiveness in height, pliability, and vascularity than that of verapamil. Moreover, the side effects such as skin atrophy, telangiectasia, and hyperpigmentation of verapamil were significantly less than those in triamcinolone *(Kuang et al., 2021).*

In this study, the histopathological examination of specimens before and after treatment with verapamil reveled that after verapamil injection showed marked reduction of collagen deposition and alteration of the fibroblast shape (from elongated to spherical).

Verhiel et al. (2015) evidenced that verapamil was found to decrease extracellular matrix production, induce procollagenase synthesis, inhibit IL6,

inhibit vascular endothelial growth factor and proliferation of fibroblast, with good efficacy, and no major side effects.

CONCLUSION

Verapamil efficacy was nearly equal to that of intralesional corticosteroid (gold standard treatment of keloids and hypertrophic scars) with avoidance of corticosteroid side effects.

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دراسة فعالية الحقن الموضعى للفيرابااميل والتريامسينولون فى علاج الندبات وآثار الجروح

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خلفيــة البحــث: النــدبات هــى خلــل جلــدي يــؤدي إلــى التشــوه و الألــم وأحيانــا الحكــة، وعلاجهــا مــا زال أمــرا محيــرا. توجــد عــدة طــرق لتحســين النــدبات منهــا الجراحــى والغيــر جراحــى والتــى تعتبــر مــن أهمهــا الحقــن الموضــعى. ويعتبــر الحقــن الموضــعي للتريامســينولون مــن أرجــح الحلــول الغيــر جراحيــة. و عقــار الفيراباميــل هــو أحــد مضــادات قنــوات الكالســيوم التــى تســتخدم لتنظــيم ضــربات القلــب، و قــد ثبــت أنــه يغيــر شــكل الخلايــا الليفيــة ويثــبط التليــف ويزيــد إنــزيم الكولاجينــاز ويــؤدي إلــى تقليــل تكــاثر الخلايا.

الهــدف مــن البحــث: مقارنــة فعاليــة الحقــن الموضــعى للفيراباميــل والتريامســينولون فــى علاج الندبات وآثار الجروح.

المرضــى وطــرق البحــث: اشــتملت الدراســة علــى 40 مــن المرضــى الــذين يعــانون مــن النــدبات، المرضــى مــن المتــرددين علــى العيــادات الخارجيــة لمستشــفى الزهــراء الجــامعي فــي الفتــرة مــن مــايو 2016 إلــى مــايو 2017 بعــد أخــذ مــوافقتهم وتــم تقســيم المرضى إلى مجموعتين متساويتين:

مجموعة أ: تم حقنها موضعيا بعقارالفيراباميل بتركيز 2.5 مجم/ملي.

مجموعة ب: تم حقنها موضعيا بعقا رالتريامسينولون بتركيز 40 مجم/ملي.

وتــم الحقــن كــل ثلاثــة أســابيع بحــد أقصــى 8 جلســات أو حتــى يســتوى ســطح الندبات أيهما أقرب.

وتم تقييم المرضى بالتصوير الفوتوغرافي قبل بدء العلاج وبعد الانتهاء منه، ومؤشر فانكوفر للندبات الذى يعتمد على ارتفاع الجرح ومرونته، وحالة الأوعية الدموية بالجرح واصطباغه.

وقد تم أخذ عينة جلد من 5 من المرضى في مجموعة أ (مجموعة الفيراباميل) قبل وبعد العلاج لتوضيح تأثيره على مستوى الأنسجة.

النتائج: كلا العقارين قد حسنا مؤشر فانكوفر للندبات و مرونة الجرح وحالة الأوعية الدموية به بدرجة متساوية تقريبا. كما أن كلا العقاريين قد حسنا ارتفاع الندبات بشكل جيد، إلا أن التريامسينولون له تأثير أكبر في تحسين ارتفاع الندبات، بينما تمييز عقار الفيراباميل في تحسين اصطباغ الندبات بشكل جيد وذلك لا يتوافر في التريامسينولون. أما علي مستوي دراسة الأنسجة فقد أكدت نتائج العينات قبل وبعد الحقن بعقار الفيراباميل كفاءته حيث قل ترسيب الكولاجين وتغيير شكل الخلايا الليفية بعد الحقن.

الاستنتاج: يعتبر عقار الفيراباميل واحد من افضل الحلول العلاجية للندبات وباقل الاسعار والاثار الجانبية.

الكلمات الدالة: الندبات، اثار الجروح، ترايامسينولون، فيراباميل.