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Efficacy and Safety of intralesional injection of verapamil in treatment of keloids

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Abstract: Objective: The aim of this study is to evaluate the efficacy of intralesional verapamil injection in treating keloids. In addition to, assessment of side effects of the therapy.

Patients and Methods: A Prospective study (Before& After) conducted for the period one year (April 2020- April 2021) at Tishreen University Hospital in Lattakia- Syria. 30 patients with keloids who received treatment with verapamil were included in the study.

Results: The mean age was 22±6.3 years, 66.7% of patients were females. Most common sites of keloids involvement were shoulders (46.7%), and acne vulgaris was the most frequently etiology (40%). A statistically significantly reduction in the means of: Vancouver Scar Scale VSS 4.66±1.9 (day 21 of last treatment) vs. 7.06±1.8 (Day 0), p: 0.0001), height (1.16±0.6 vs. 2.23±0.6, p: 0.001), and pliability (1.33±0.9 vs. 2.60±0.6, p: 0.003), without recurrence of keloids at the day 90 of the last treatments. Burning pain was the most side effect frequently seen (98%).There was no significant relationship between clinical improvement and each of the following: duration of disease and age of the patient (p>0.05).

Conclusion: Verapamil has significant therapeutic effects in decreasing the height of the lesion, improving pliability without recurrence of lesions or serious adverse effects, thus, it could be a safe choice in treatment of keloids.

Keywords: Keloids, verapamil, Vancouver.

فعالية وأمان علاج الجدرات بالفيراباميل حقناً ضمن الآفة

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المستخلص: هدفت الدراسة إلى تقييم فعالية الحقن الموضعي للفيراباميل ضمن الآفة في علاج الجدرات، بالإضافة لتحديد الآثار الجانبية الناتجة عن هذا العلاج.

طريقة البحث: كانت هذه دراسة مستقبلية (قبل، بعد) أجريت في مشفى تشرين الجامعي في اللاذقية- سوريا خلال الفترة الممتدة ما بين نيسان 2020- نيسان 2021. شملت الدراسة 30 مريضاً لديهم جدرات ممن تلقوا العلاج عن طريق حقن الفيراباميل ضمن الآفة.

النتائج: بلغ متوسط العمر 22±6.3 سنة، 66.7% من المرضى هم من الإناث. كانت إصابة الكتفين هي الأكثر تواتراً (46.7%)، والعد الشائع هو السبب الأكثر شيوعاً للجدرات (40%). حدث تناقص هام احصائياً في كلٍ من: متوسط مقياس فانكوفر (4.66 ±1.9 (اليوم 21 من الجلسة الاخيرة) مقابل 7.06 ± 1.8 (اليوم 0قبل العلاج)، p: 0.0001)، درجة الارتفاع (1.16 ±0.6 مقابل 2.23 ±0.6، p: 0.001)، ودرجة القساوة (1.33 ±0.9 مقابل 2.60 ±0.6، p: 0.003) ، من دون حدوث نكس الجدرة في اليوم 90 من نهاية العلاج، دون أي تغير هام في درجة التصبغ والتوعية. كذلك حدث تناقص هام في درجة الحكة والألم (p<0.05) في نهاية العلاج. بدراسة الآثار الجانبية للعلاج فإن

الألم الحارق هو الأكثر تواتراً (98%)، ولم يلاحظ وجود علاقة ذات دلالة احصائية بين التحسن السريري وكل من عمر المريض أو عمر الجدرة ($p<0.05$).

الاستنتاج: يملك الفيراباميل تأثيرات علاجية هامة في إنقاص ارتفاع الآفة، تخفيف درجة القساوة من دون حدوث النكس أو تأثيرات جانبية خطيرة، وبذلك قد يكون خياراً آمناً لعلاج الجدرات.

الكلمات المفتاحية: الجدرات، الفيراباميل، فانكوفر.

Introduction.

Keloids represent an area of benign overgrowth of fibrous tissue that usually develops after healing of a skin injury, and extends beyond the original defect [1].

The exact incidence of keloids is unknown. They affect men and women equally especially younger individuals with an average age at onset is 10- 30 years. Familial predisposition has seen in some patients[2, 3].

The pathogenesis of keloids remain unclear completely. The leasion develop mostly due to combination of several factors including trauma, inflammation and genetics[4]. Overexpression and/or inadequate regulation of growth factors such as transforming growth factor –beta (TGF- beta) may play a role in the keloids formation. In addition, the reduction in the production of molecules that promote breakdown of matrix, increase the activation of signals for insulin like growth factor- 1 (IGF- 1), and decrease the rate of fibroblast apoptosis are considered as predisposing factors [5, 6].

Keloids often occur on the chest, upper back, shoulders, and more frequently on ear lobes[7]. They vary from nodules to plaques, and often cause intense itching, pain, skin infection and aesthetic problems especially during growth phase, leading to a significant burden for patients and severe psychological problems[8]. Although there are multiple treatments options for clinicians including medical and surgical methods, none of them has proven completely effective, with high recurrence rate. Consequently, treating keloid scars continue to be particular challenge for the dermatologists[9].

Verapamil is a calcium channel blocker that inhibit the synthesis and secretion of extracellular matrix, induce synthesis of procollagenase and inhibit interleukin- 6 (IL- 6), (Vascular endothelial growth factor VEGF, Transforming growth factor- b1 TGF- β1 and cellular proliferation of fibroblasts, resulting in depolymerization of actin filaments, alteration of cell shape, apoptosis and reduction of fibrous tissue production[10]. Many controlled clinical trials have demonstrated that verapamil is clinically safe and less side effects than other medications in treatment of keloids.

Therefore, the objectives of the study were to: 1- determine the therapeutic efficacy of verapamil in the treatment of keloids. 2- evaluate the association between the response to treatment and duration of keloids. 3- evaluate the association between the response to treatment and age of the patients. 4- assessment the side effects of treatment.

Patients and Methods:

This is a Prospective study (Before & After) of a group of patients with keloids attending the Dermatology Department's outpatient clinic at Tishreen University Hospital in Lattakia- Syria during a one year period (April 2020 to April 2021). The following data were recorded: demographic data (age, sex), position and age of keloids. Exclusion criteria were patients with one of the following: pregnancy or lactation, local infection, previous history of treatment with other modalities of therapy during the last six months, and patients with cardiovascular diseases. The site of injection was sterilized by povidone iodine solution, then verapamil 2.5 mg/ml was administered intralesionally until complete blanching of the lesion was achieved, the dose was between (0.5- 1.5 ml). Every patient has received a session every 21 days interval, for a maximum of 6 sessions, and patients were followed up at the day 21 of last treatment and at the day 90 of the last treatmemt.. Assessment was done by using clinical photograph and we measure the height with Caliper, at the Day 0, the day 21 of last treatment and at the day 90 of the last treatmemt, which evaluated by Vancouver Scar Scale (VSS). VSS includes four components:

Pigmentation (0- 2): normal 0, hypopigmentation 1, hyperpigmentation2

Vascularity (0- 3): normal 0, pink 1, red 2, purple 3

Pliability (0- 5): normal 0, supple 1, yielding 2, firm3, banding 4, contracture 5

Height (0- 3): normal (flat)0, 0- 2 mm 1, 2- 5 mm 2, >5 mm 3. [11]

The clinical response was graded according to the percentage reduction in VSS into: mild: 1- 25%, good: 26- 50%, very good: 51- 75%, excellent>75%. Adverse effects associated with treatment like pain during injection, dermal atrophy, telangiectasia were also collected.

Ethical consideration: After discussing the study with the patients, all of them gave a complete and clear informed consent to participate in the study.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations (SD), median, Frequency and percentages. Differences of distribution examined by using Fisher exact test. Wilcoxon test was used to compare two paired groups, and One way analysis of variance (Anova) to compare responses across groups. P value <0.05 was considered as statistically significant

Results.

A total of 30 patients with keloids who presented to the Department of Dermatology from April 2020 to April 2021 participated in the study. The baseline characteristics of patients are as given in table (1). The mean age of patients who enrolled in the study was 22±6.3years, 66.70% of the patients were

females. The most common sites of keloids involvement were shoulders (46.7%), and median duration of disease was 15 months. Acne vulgaris represented the most common cause of keloids (40%).

Table (1) Demographic characteristics of the study population

Variables	Result
Age (years)	22±6.3 (11- 36)
Sex	
Male	10 (33.30%)
Female	20 (66.70%)
Sites of keloids	
Shoulder	14 (46.7%)
Sternum	6 (20%)
Lower part of back	4 (13.3%)
Other sites (face, abdomen, lower limb, humerus, earlobe, back)	6 (20%)
Age of the keloid (months)	(8- 60), average 15 months
Etiology of keloids	
Acne vulgaris	12 (40%)
Surgery	8 (26.7%)
Spontaneous	7 (23.3%)
Burn scar	2 (6.7%)
Ear piercing	1 (3.3%)

For the Vancouver scale parameters, there was a significant reduction in height, and pliability at day 21 after the last session (1.16±0.6 vs. 2.23±0.6, p: 0.001) and (1.33±0.9 vs. 2.60±0.6, p: 0.003) respectively. This reduction was maintained at t day 90 in the study population. There was no significant reduction in pigmentation and vascularity (p>0.05). There was a statistically significant reduction in VSS at **Day 21 of last treatment** (4.66±1.9 vs. 7.06±1.8, p: 0.0001), and maintained at **Day 90 of last treatments**, and percentage reduction in VSS score was 34% table (2).

Table (2) Results from assessment of keloids photos

Variable	Follow up			P value
	Baseline Day 0	Day 21 of last treatment	Day 90 of last treatments	
1- VSS parameters				
Height	2.23±0.6	1.16±0.6	1.16±0.6	0.001
Vascularity	1.56±0.9	1.50±0.9	1.50±0.9	0.1
Pliability	2.60±0.6	1.33±0.9	1.33±0.9	0.003
Pigmentation	0.9±0.6	0.9±0.6	0.9±0.6	0.3
2- VSS	7.06±1.8	4.66±1.9	4.66±1.9	0.0001

The response to treatment for all 30 patients was as the following: mild: 7 (23.3%), good: 18 (60%), very good: 3 (10%), and excellent: 2 (6.7%) Figure1.

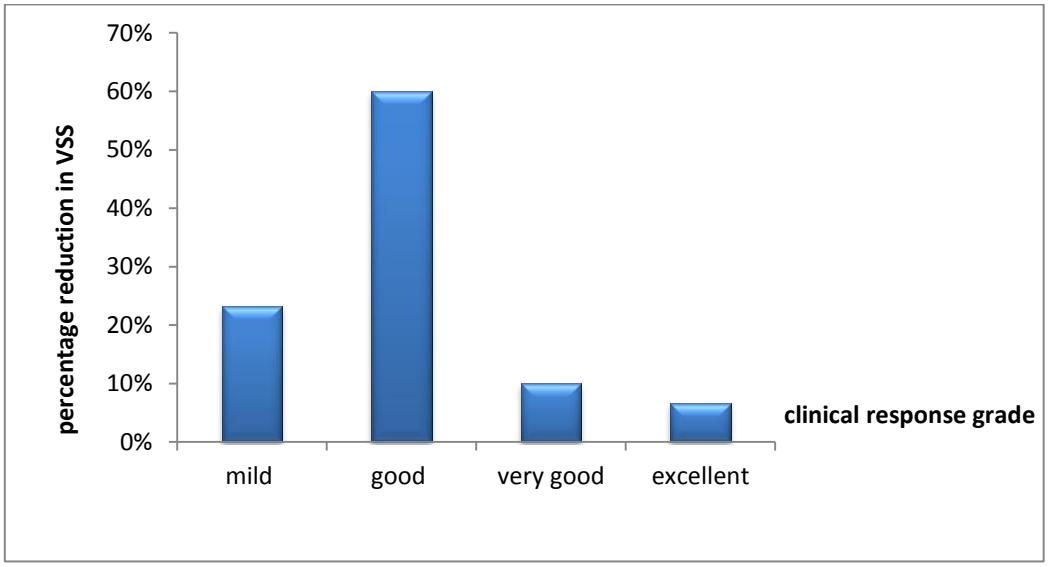

Figure (1) clinical response to treatment according to the percentage reduction in VSS

There was a significant improvement in pain and itchiness between baseline and at third week (1.33±1.2 vs.0.8±0.76, p: 0.005) and (1.23±0.7 vs. 0.56±0.50, p: 0.001) respectively.

As shown below in table (3), there was no correlation between response to treatment and each of the following: age of the patients (p: 0.8) and duration of the keloids (p: 0.7).

Table (3) The Association between response to treatment and (age of patients, age of keloids)

Variable	Mild	Good	Very good	Excellent
Age group (year)				
≤20	4	9	2	**2**
>20	3	9	1	**0**
Onset of keloids (year)				
≤1	2	11	2	**1**
>1	5	7	1	**1**

The only side effect experienced by patients was burning pain in 98% of the patients. It last few hours after injection.

Discussion.

Since the pathogenesis of keloids is not completely known, there is a lack of consensus on an ideal regimen of treatment keloids, and the need for adequate, effective therapy is necessary. There are number of clinical studies about the efficacy and safety of verapamil in treating keloids which revealed promising results. [14]

The present study demonstrated that keloids were more frequently in females possibly secondary to the cosmetic implications associated with disfigurement, younger patients, and the most sites frequently affected were shoulders. There was a significant response to verapamil injection therapy in

keloid scars, and the most notable effects were improvement in height and pliability, with no significant changes in pigmentation and vascularity. There was a significant improvement in pain and itchiness, and the only side effect of treatment was burning pain.

Anti –fibrotic activity of verapamil may explain its potential for treatment keloids. Alterations in fibroblasts include reorganization of actin filaments, inhibition of collagen synthesis, increased secretion of matrix metalloproteinase- 1, decreased production of interleukin- 6, reduced cell proliferation and increased apoptosis[12].

Shanthi *et al.*, 2008 showed reduction in vascularity, pliability and width of keloid scar after 3 weeks of treatment with intralesional injection verapamil, without significant effect on pigmentation, and these changes were present at one year of follow up [13].

Shah *et al.*, 2018 demonstrated that intralesional injection verapamil gives very good to excellent improvement in 40% of patients with percentage reduction in VSS score 46.21%. The only observed side effects was post- procedure pain in almost all patients[14].

Saki *et al.*, 2019 showed that there was a reduction in height and pliability of the keloid scars at the end of study ($p<0.001$), without significant changes in vascularity and pigmentation ($p>0.05$)[15].

Khattab *et al.*, 2019 also demonstrated statistically significant improvement in the height and pliability of the keloids. The observed side effects were recurrence of keloids in two cases and hypopigmentation in one case [16].

The results of the current study are comparable to the findings reported by previous studies.

In summary, treatment of keloids with verapamil could achieve better efficacy with less adverse effects.

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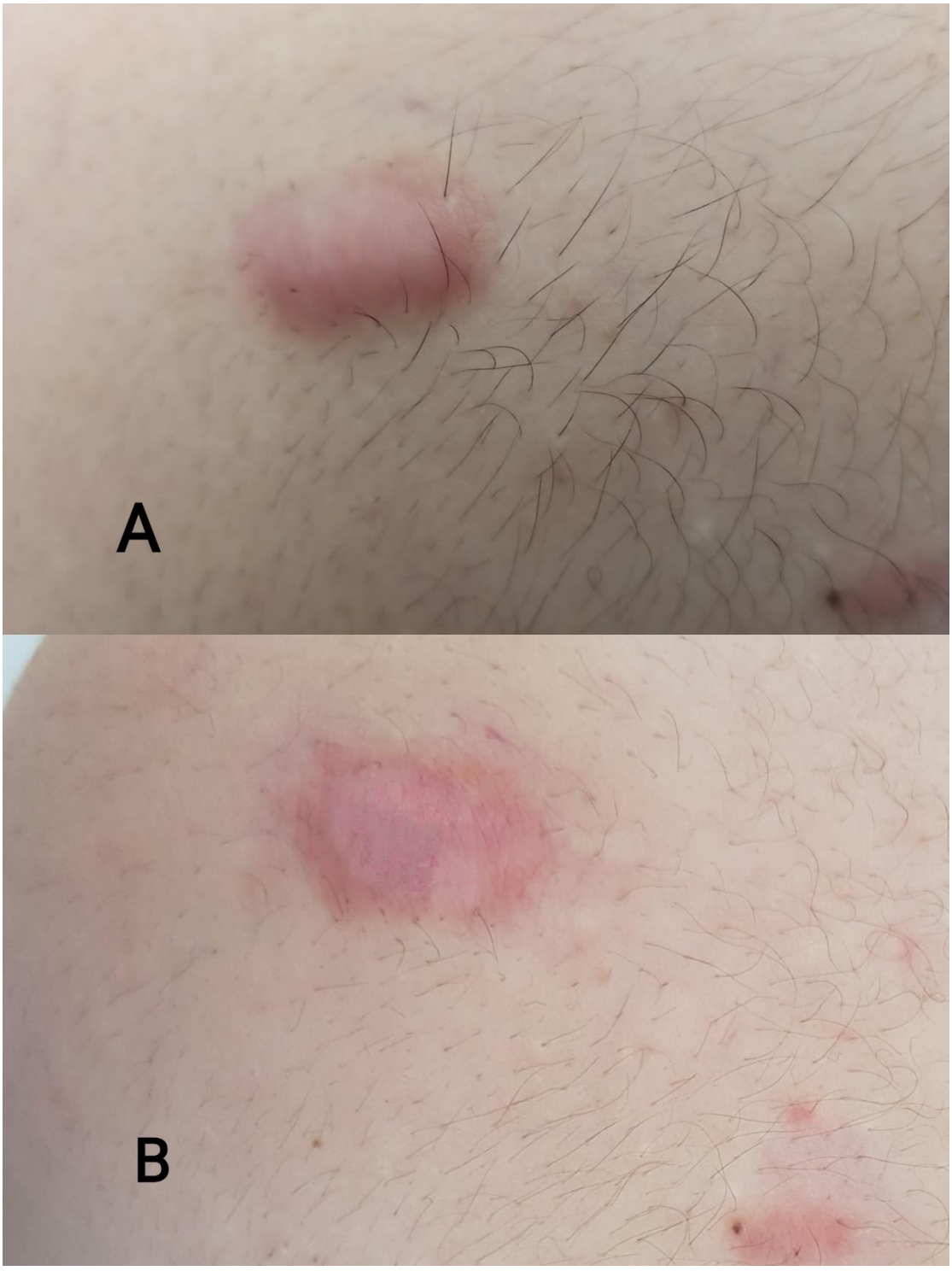

Figure 2: the figure shows the keloid A = Before treatment, B= After 21 weeks of treatment (excellent response).