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Intralesional Verapamil As A Treatment Option For Pinna Keloids

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I. Introduction

Keloid and hypertrophic scars are two common conditions seen in surgical specialties outpatient departments because of impairment in the wound healing process. Keloid is benign tissue that arises from fibroblast proliferation following skin injury. The common sites include the trunk, head and neck regions. In the head and neck region pinna is among the frequent sites with an incidence of 2.5% following ear piercing.[1] In the Indian population, the incidence of pinna keloid is 10-20 %, with female preponderance mainly because of the practice of multiple ear piercings to adorn jewelry. Though asymptomatic in most of the patients, cosmetic concerns bring the patients to the OPD seeking management.[2,3]

Multiple treatment options are available such as surgical excision followed by primary closure or repair of primary defect, intralesional injection using various agents, topical agents and radiotherapy. Surgical excision can be considered as an elective treatment plan. Still, the disfigurement due to tissue loss can be troublesome at times, especially if the size of the lesion is small. The role of an intralesional agent is important in this context. The widely used class of drugs is corticosteroids and among steroids, the well-known drug that is considered first line is triamcinolone. The other less frequently used ones are 5-Fluorouracil and hyaluronidase. Imiquimod is a novel topical immunomodulator used to treat superficial skin malignancy. The same has now shown to be effective in scar management as well.[2,4,5]

Triamcinolone acts on the keloid by its anti-inflammatory properties. Intralesional steroids are less effective in large keloids. In such cases, surgery is considered as the primary treatment. The recurrence rate of keloid is around 20% even after surgery. Intralesional injections at the surgical site once the wound is healthy is considered to prevent or reduce the rate of recurrence. Serial triamcinolone injections have been reported to have side effects such as pain and discoloration at the site due to dermal atrophy. The other option to reduce the recurrence is very low-dose radiation to the keloid.[5]

Hyaluronidase is another intralesional agent used as a single drug or in combination with steroids. It hydrolyzes high molecular weight hyaluronic acid which has inflammatory, fibrogenic and angiogenic properties.[5]

Verapamil, an antiarrhythmic agent belonging to the class of calcium channel blockers has recently been found to have scar-enhancing properties owing to its action on inflammatory response in the wound healing process. The possible main mechanism of action of verapamil is by altering fibroblastic pathways. The drug acts locally on various intracellular and extracellular pathways directly as well as indirectly, thereby inhibiting the proliferation of fibroblasts at wound sites with possible interaction with Interleukin-6. Verapamil was also found to enhance the production of pro collagenase which further led to degradation of the extracellular matrix. It was also found to decrease platelet aggregation, decrease production of angiogenic factors, disrupting polymerization of actin filaments leading to cell conformal changes and ultimately causing apoptosis. All these actions collectively inhibit the production of fibrous tissue. Intralesional verapamil has been noted to have fewer adverse effects as compared to triamcinolone and is more cost-effective as well .[6,7]

The present study aimed to evaluate the efficacy of verapamil as a scar-modulating agent. We used the Patient and Observer Scale Assessment Scale (POSAS) scoring system to assess the treatment outcome, as this is the only scoring system that considers the patient's complaints related to the disease.[8]

II. Materials And Methods

The study was conducted at two tertiary care centers in the southern part of India. After obtaining ethical committee clearance from the institutions, each author randomly selected 20 pinna keloid cases who were willing to take part in the study and were divided into two groups. Group TH received a combination of triamcinolone and hyaluronidase injections once in two weeks for two months, ie., 4 injections as a complete treatment schedule. The group V received an injection of verapamil (2.5mg/ml) with the injection schedule the same as that of group TH. In both the groups complete blanching of the keloid was considered as the end point of a dose. Patients who were non-compliant and who had not completed all four doses were excluded from the study. Patients from both groups who had not shown improvement were advised to undergo excision. The Patient and Observer Scar Assessment Scale (POSAS) scoring sheet was given to the patients before the initiation of treatment and 8 weeks after completion of the treatment (Table 1). The data were entered into Microsoft Excel and analyzed using SPSS software version 10.

All procedures performed in this study were in accordance with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this research work.

Table 1

	Patient scar assessment scale									
No, No Complaints	1	2	3	4	5	6	7	8	9	10
Is the scar painful?										
Is the scar itching?										
No, as normal skin	1	2	3	4	5	6	7	8	9	10
Is the colour of the scar different?										
Is the scar more stiff?										
Is the thickness of the scar different?										
Is the scar irregular?										
Total Patient score										
	Observer scar assessment scale									
	1	2	3	4	5	6	7	8	9	10
Vascularity-										

Pale/Pink/Red/Purple/Mix										
pigmentation-Hypo/Hper/Mix										
Thickness										
Relief										
Pliability										
Surface area										
Total Observer score										
Total POSAS score										

III. Results

40 patients with keloid of the pinna, of the age group 18-41 years were included in the study (Table 2). Out of 40, 38 were females and two were males. Keloids above the orbitomeatal line were considered as lesions in the upper part of the pinna and below the line as the lower part of the pinna. The keloid of the lobule of the pinna was considered separately. Details of site-wise distribution are given in (Table 3). Most of the patients had only one keloid at the time of presentation. 4 patients had two keloids and one had three at the time of OPD visit. For the study purpose, intralesional injection treatment was advised for only the smallest-sized keloid and the larger ones were surgically excised. 36 out of 40 patients had multiple ear piercings and 4 had previous history of keloid on the opposite side. 4 patients had a family history of keloid or hypertrophic scar.

The patient (Pt) and observer (O) scale values in the POSAS were analyzed separately using paired t-test and it found that there was a significant difference in the S and total (T) score in pre-OP ($P<0.05$). However, there were no differences in the post-OP scores (Table 4 and Figure 1-3).

The treatment outcomes were analyzed in each group and found that both treatment regimens were equally effective (Table 5 and 6).

Table 2

Age group (In years)	Number of patients
18-22	6
23-27	22
28-32	5
33-37	4
38-42	3

Table 3

Site of pinna keloid	Number of patients
Upper part	28
Lower part	11
Lobule	1

Table 4

	Group	Mean (SD) Pre OP	P value	Mean (SD) Post OP	P value
Patient scale	Group TH	38.8 (3.8)	0.078[a]	24.3 (2.9)	0.478[a]
	Group V	37.2 (3.5)		23.7 (1.8)	
Observer scale	Group TH	32.6 (4.7)	0.027[a]	18.4 (1.6)	0.599[a]
	Group V	29.9 (2.5)		18.1 (1.9)	
Total POSAS	Group TH	71.5 (6.1)	0.009[b]	42.6 (3.8)	0.433[a]
	Group V	67.1 (3.8)		41.8 (2.9)	

a-statistically insignificant, b-statistically significant.

Table 5

	Group	Mean (SD) Pre OP	Mean (SD) Post OP	Mean difference	P-value
Patient scale	Group TH	38.8 (3.8)	24.3 (2.9)	14.6	<0.001[a]
	Group V	37.2 (3.5)	23.7 (1.8)	13.5	<0.001[a]
Observer scale	Group TH	32.6 (4.7)	18.4 (1.6)	14.3	<0.001[a]
	Group V	29.9 (2.5)	18.1 (1.9)	11.9	<0.001[a]

Total POSAS	Group TH	71.5 (6.1)	42.6 (3.8)	28.9	<0.001[a]
	Group V	67.1 (3.8)	41.8 (2.9)	25.3	<0.001[a]

Table 6

	Group	Mean (SD) difference	Difference in difference	T	P-value
Patient scale	Group TH	14.6 (4.2)	1.1	0.82	0.419
	Group V	13.5 (4.3)			
Observer scale	Group TH	14.3 (5.7)	2.5	1.6	0.107
	Group V	11.9 (3.4)			
Total POSAS	Group TH	28.9 (8.6)	3.6	1.6	0.123
	Group V	25.3 (5.2)			

Figure 1

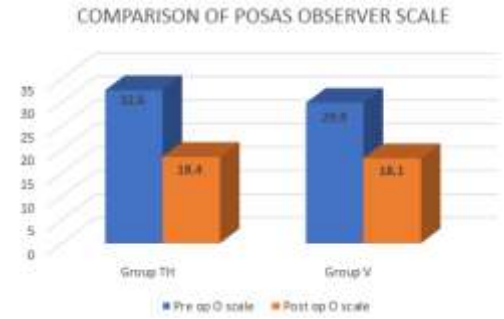


Figure 2

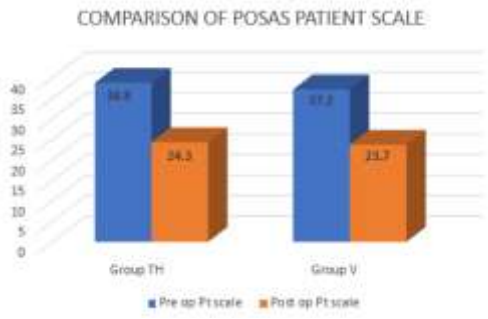
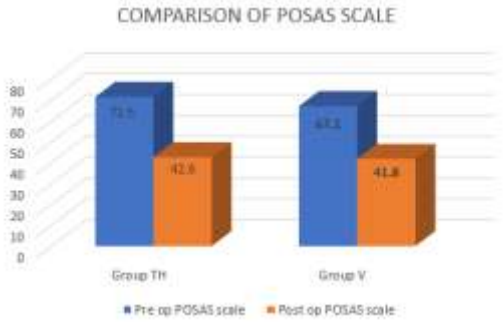


Figure 3



IV. Discussion

Keloid by definition extends beyond the borders of the original wound as compared to a hypertrophic scar which is confined to the dimensions of the wound. Considered as a fibroproliferative lesion, the most common sites are the chest, shoulder, neck and ear [1,4]. Studies have shown that the female gender may have a

predilection for the occurrence because of physiological factors. Noishki et al in the study concluded that female gender and puberty are independent risk factors. Similarly, in our study the majority of the patients were in the age group 18-30 years and females outnumbered the males [9].

The exact mechanism of keloid formation is not clearly understood but the presence of a triggering event, most commonly a traumatic event of the skin, appears to be the most common initiating point in susceptible individuals. In our study all the patients had a history of their ears being pierced. Helix was the common site in our study and it's in accordance with other similar studies. Family history is also considered as a risk factor. In our study group, there were 4 patients with a family history of impaired wound-healing mechanisms. Lobule, which is considered a rare site, was seen in one patient who had a genetic predisposition.

An important factor in the selection of keloid treatment is the patient's expectations. The majority are asymptomatic and seek medical attention for cosmetic reasons. In such cases, a wide excision that results in a large primary defect may not be the best option. Proper counseling, explaining the pros and cons of each treatment option is of utmost importance. Tissue loss associated with surgical techniques in management makes the patient consider intralesional therapy as the initial option. The various intralesional drugs used commonly are steroid agents, bleomycin, mitomycin and hyaluronidase. Recently cryotherapy has also been found to be effective in managing problems associated with impaired wound healing. The steroidal agent triamcinolone is considered the standard therapeutic drug either alone or in combination with other non-steroidal agents in the management of keloid and hypertrophic scar. There is no consensus regarding the dose, frequency, or duration of intralesional agents available at present. Another debatable area is the candidate profile for surgical management. Few studies suggest excision of keloid followed by intralesional therapies at the surgical site to prevent recurrence. However, few studies have shown surgery equally effective as intralesional therapy with triamcinolone and hyaluronidase.

The combination of hyaluronidase and triamcinolone is considered one of the standard treatment options in keloid management. The use of this combinational therapy was found to be effective in our study as well with significant differences in preoperative and postoperative POSAS scale.

The use of verapamil as a single agent for the management of keloid has not been evaluated. However, studies conducted by Shah YM et al, Uzair et al and Shanti et al have shown that verapamil can be used as an intralesional agent [10,11,12]. Shah et al and Kant SB et al used a 3-dose schedule whereas Shanti et al followed an 8-dose schedule [10,13]. The usefulness of multiple dosing schedules has to be evaluated in detail. We used a 4-dose schedule for two months.

Bilal et al carried out verapamil therapy in a total of 144 patients with a treatment duration spanning over 16 weeks and concluded that verapamil and non-verapamil agents exert equal treatment outcomes [14]. Animal studies have proven that verapamil suppresses fibroblastic proliferation. In vitro cell studies have shown that verapamil exerts a dose-dependent effect in inhibition of fibroblast multiplication, and reduction in collagen and extracellular matrix deposition. The most common side effects of verapamil therapy are pain at the local site, dermal atrophy, and hypopigmentation. In our study, few patients complained of pain at the injection site. No other reported adverse effects were noted.

Studies show verapamil in combination with other agents especially triamcinolone has more improved results as compared to monotherapy. All these prove that treatment regimens which include verapamil is an effective option in scar management. Our study supports the use of verapamil as a single agent and shorter treatment duration in the treatment of pinna keloid.

V. Conclusion

The authors would like to conclude that intralesional verapamil can be considered as a single scar modulatory agent for the treatment of small to medium-sized keloids in pinna. Though the study population was small, the treatment outcome with verapamil was at par with the combination of triamcinolone and hyaluronidase. We would also like to emphasize the need for a larger study incorporating treatment with verapamil for keloids of other anatomical sites.

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