Original Research Article

DOI: http://dx.doi.org/10.18203/2349-2902.isj20194076

Recurrence of keloids after application of epidermal growth factor

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Received: 21 May 2019 Revised: 06 August 2019 Accepted: 07 August 2019

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ABSTRACT

Background: Exact aetiology for keloid formation is yet unknown. The prime goal of the therapy is to decrease the process of scarring. Many modalities of treatment are available for keloids. With current treatment modalities, recurrence rates approaches 75%. This study was conducted to find out whether application of Epidermal growth factor will reduce recurrence rates of keloids, after surgical excision.

Methods: An observational study was conducted by collecting details of 40 patients who underwent surgical excision of keloids followed by epidermal growth factor application over the wounds. The patients have been followed up to 6th months post excision and recurrence rates of keloids as well as overall scar quality were analysed.

Results: Out of 45 patients included in the study, 16 (35.6 %) were males and rest females. The median age of the study population was 18.0 (with an IQR 16.0; 26.0). Out of 45 patients, 12 patients had family history of keloids (73%). Out of 45 patients, 8 had keloid tendency which amounts to 82%. Out of 45 patient who underwent treatment, 22 patient developed recurrence which is 48.9% Out of 45 patients included in the study, 16 (35.6 %) were males and rest females. The median age of the study population was 18.0 (with an IQR 16.0; 26.0). Out of 45 patients, 12 patients had family history of keloids (73%). Out of 45 patients, 8 had keloid tendency which amounts to 82%. Out of 45 patient who underwent treatment, 22 patient developed recurrence which is 48.9%.

Conclusions: There is a dearth of randomized controlled trials supporting the efficacy of epidermal Growth factor in preventing keloid recurrence. The subjective improvements seen in some cases are encouraging. This study will be a foundation for future studies and will highlight the breadth of knowledge yet to be explored by this therapy.

Keywords: Keloid, Excision, Epidermal growth factor, Recurrence rates

INTRODUCTION

Scar following trauma and surgeries are a major problem world-wide. Aberrations of normal physiologic wound healing and may cause excessive scarring which may develop after any insult to the deep dermis, including burns, infections, trauma, vaccines, piercing and surgeries. Patient's quality of life is affected due to the psychological trauma associated with excess scarring and symptoms like pruritus, pain and contractures.

No treatment modality is uniformly successful for keloids. Despite of high recurrence, patients demand for

intervention due to physical and psychological burden of the disease. Pruritus and pain are the main symptoms. Excision of a keloid and primary closure invariably result in recurrence. Available adjuvant therapies are intralesional steroid injection, radiation, cryotherapy, laser, and immunomodulatory agents. Intralesional corticosteroid injection therapy is accepted as the first line in treatment for keloids. It also has synergistic effects with other modalities. Rapidly proliferating lesions respond best to steroid injection than slowly growing, mature lesions. In some studies, Intraoperative and postoperative intralesional steroid therapy following excision has been shown to reduce recurrence to around 50 %. Numerous retrospective studies have shown that a short course of

low-dose radiotherapy to the keloid excision wound immediately after excision has been shown in to reduce the rate of recurrence. The risks of ionizing radiations including the potential for malignant transformation, warrants caution and the need for further study. In adults with lesions refractory to other modalities, radiation therapy still offers a chance. Cryotherapy is now accepted as a low-cost and effective method of treating keloid scar. When treated with liquid nitrogen, complete flattening or greater than 80% volume reduction occurred in 73-85% of lesions are shown in multiple prospective studies. 1, 2 The effect of lasers in keloids have been studies for years but large multi-centric studies are lacking Though in clinical practice laser is well accepted modality for treating all types of scars, clinical studies quantifying its effectiveness is still lacking. Availability of many varieties of therapeutic lasers also complicates the matter.³In summary, there is no single modality completely effective in keloid management, multimodality approaches offer some promise and treatment should be individualized according to patients needs and expectations. In current management protocols, first line is corticosteroids, silicone sheeting, and compression garments. 4 Large, recalcitrant keloids can be managed by surgery, steroids, radiation, or other modalities and may best be performed.

Epidermal growth factor (EGF) is a 6045 Da protein with 53 amino acid residues and three intra-molecular disulfide bonds. The discovery led to the Nobel Prize for Stanley Cohen.⁵ It is synthesized by platelets and macrophages and stimulates collagenase secretion by fibroblasts to remodel matrix.6 This growth factor is important in initiating cell migration in normal wound healing.⁷ It is found to be involved in positive regulation of cell proliferation, angiogenesis, ECM biosynthesis, and cell motility enhancing proper wound healing. EGF might be useful to treat keloid scars, especially to prevent occurrence rather than treatment of keloids already in place.8 Recombinant human EGF is approved to be used in humans for treating diabetic foots and superficial burns and is found to be safe for local application. Local application of recombinant Human epidermal growth factor in keloid excision wound site may promote proper epithelial and fibroblast proliferation and fast remodelling of wound leading to a healthier scar.

Objectives

The objective of this study is to find out the recurrence rates of keloids with application of epidermal growth factor after excision and to find out if there is improvement in scar quality in terms of POSAS score, with application of epidermal growth factor in post-excision keloids.

METHODS

Prospective study design was used to conduct a study in Department of Plastic and Reconstructive Surgery of Government Medical College, Thiruvananthapuram, from July 2017 to December 2018. Sample size was calculated as followed.

The recurrence rates of keloids after excision and closure ranges from 45-100 %. ^{4,5}

Sample size is calculated by the following formula

$$n=\frac{4PQ}{\eta^2P^2}$$

where P=reference recurrence rate 70%, Q=(1-P), η (Relative precision)=20%, Confidence interval=95%, substituting all values, n=45.

Data collection tool: Data was collected from patients using a semi structured questionnaire.

Data analysis

Appropriate statistical software (SSPS trial version) was used for analysis of data. All quantitative variables were expressed as mean (SD) and all categorical variables as proportions. Paired t-test was used for determining associations. A p value less than 0.05 will be considered as statistically significant. Scar quality assessment was done using patient and observer scar assessment scale (POSAS).

Data collection process

All patients undergoing elective keloid surgery who was in age group between 10-60 years, who gave informed written consent and who didn't undergo any other modality of treatment for last two months were included in the study. Patients with wound infection, diabetes, immune compromised status like AIDS/HIV infections and malignancy chemo-radiation were excluded from the study. Skin conditions like eczema, psoriasis and other autoimmune diseases were excluded. Patients with conditions affecting proper wound healing like smoking, scurvy, and collagen vascular diseases were also excluded. Patients who were pregnant were excluded. Keloids younger than 3 months were excluded, no upper limit for duration of occurrence. The merits and demerits of each available modality of treatment are explained based on current norms of managing keloids. Those who opt in were included in the study. A detailed history of each patient obtained starting with history of keloid formation, recurrence, previous treatments coexisting, co-morbid conditions like; diabetes mellitus, hypertension and jaundice, family history of keloid were asked. Both physical measurement and photographic documentation of keloid were done. Preoperatively all patients should undergo routine lab tests were done before any surgery. No preoperative hair clipping or shaving were done in the area. After painting with 5% povidone iodine, local anaesthesia was given with 1% lignocaine with adrenaline if not contraindicated. Keloid

lesions were excised completely through the junction of keloid and normal skin, not leaving behind any keloid tissue. Perfect haemostasis attained. 1 ml/cm2 of epidermal growth factor gel containing recombinant human epidermal growth factor was applied over the entire raw area. Wound was closed with 4-0/6-0 nonabsorbable suturing of skin. No subcutaneous sutures were placed. The treatment of wound with rEGF will be continued for 1 week after the surgery by applying gel over the wound every alternate day. No other treatment modality was followed during this treatment. Wounds were inspected by a senior plastic surgeon after 3 months and 6 months post excision. Treatment outcome was recorded as recurrence or no recurrence. Complications if any were also recorded. No recurrence was defined as scar without elevation and extension, although slight scarring or redness present was accepted as no recurrence. Recurrence was defined as any elevation of the scar above normal skin or extension beyond the original surgical wound. No major complications were observed from the study.

RESULTS

Out of 45 patients included in the study, 16 (35.6) were males and rest females (Figure 1). The median age of the study population was 18.0 (with an IQR 16.0; 26.0) (Table 1). Of these patients, keloids were caused by ear piercing in 22 patients, following surgery in 11 patients and rest due to trauma. 62 patients had associated wound

complications leading to keloid formation (Figure 2). Median duration of keloids were 2 years (with an IQR 1.00; 4.00). Out of 45 patients, 12 patients had family history of keloids (73%) (Table 2). Out of 45 patients, 8 had keloid tendency which amounts to 82% (Table 3). 23 patients underwent prior treatment for keloids of which 15 were given intralesional steroids and 10 underwent surgery (Figure 3).

Table 1: Age distribution of patients.

Age (years)	Incidence	%
10-19	25	55.56
20-29	10	22.22
30-39	2	04.44
40-49	5	11.11
50-59	3	6.67
Total	45	100.0

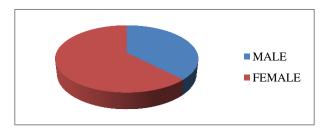


Figure 1: Sex distribution.

Table 2: Family history of keloids.

	Frequency	Percent	Valid percent	Cumulative percent
No	33	73.3	73.3	73.3
Yes	12	26.7	26.7	100.0
Total	45	100.0	100.0	

Table 3: Keloid tendency.

	Frequency	Percent	Valid Percent	Cumulative percent
No	37	82.2	82.2	82.2
Yes	8	17.8	17.8	100.0
Total	45	100.0	100.0	

Table 4: Recurrence of keloids.

	Frequency	Percent	Valid Percent	Cumulative percent
No	23	51.1	51.1	51.1
Yes	22	48.9	48.9	100.0
Total	45	100.0	100.0	

Table 5: Comparison of gender with recurrence rates.

Gender	Total (n=45)	No recurrence (n=23)	Recurrence (n=22)	P overall
		-		0.007
Male (%)	16 (35.6)	13 (56.5)	3 (13.6)	
Female (%)	29 (64.4)	10 (43.5)	19 (86.4)	

Table 6: Comparison of recurrence with aetiology.

	Total (n=45)	Ear piercing (n=16)	Second stud (n=6)	Surgery (n=11)	Trauma (n=12)	P overall
Recc:						0.059
No (%)	23 (51.1)	4 (25.0)	3 (50.0)	8 (72.7)	8 (66.7)	
Yes (%)	22 (48.9)	12 (75.0)	3 (50.0)	3 (27.3)	4 (33.3)	

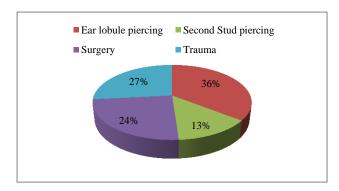


Figure 2: Etiological correlation.

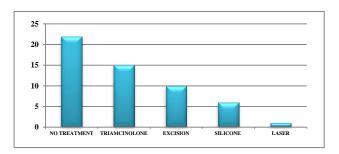


Figure 3: Previous treatment histories.

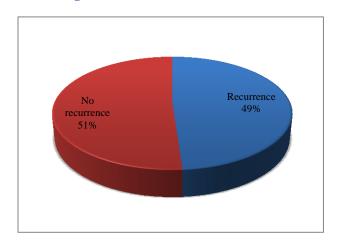


Figure 4: Recurrence of keloids after current therapy.

Out of 45 patients recurrence rate in males were 43.5% while recurrence rates in females were 86.4%. (p overall 0.007). Out of 23 males, 52.2% had wound complications while females had wound complication rate of 22.7% (p=0.084). Average duration of keloids in males were 2.00 years (with IQR-1.00; 4.00) and in females it was 4.00 (IQR-1.25; 6.00). Males gave a family history rate of 17.4% while females gave a family history of 36.4%.

Keloid tendency in males was 17.4% while in females it was 18.2%. Out of 45 patient who underwent treatment, 22 patient developed recurrence which is 48.9% (Table 4, Figure 4).

DISCUSSION

This study was conducted in Plastic Surgery Department of Government Medical College Thiruvananthapuram to determine the effect of epidermal growth factor on keloid recurrence. Duration of study was for one and a half year. 45 patients underwent surgical excision of keloids followed by application of epidermal growth factor over surgical wound in the immediate post-operative period. Recurrence of keloids was assessed at 3 months and 6 months periods and analysed.

In our study population more of females were present. 62% were females and 37% males. In literature, prevalence of keloids is equal in both sexes. Increase in female number in our study may be because of the common practice of ear piercing in this region and increased cosmetic concerns in females. More over ear piercing is usually done by goldsmiths rather than medical professionals in a hospital setup. The median age of the study population was 18.0 (with an IQR 16.0; 26.0). Majority of patients in the study group falls in younger age groups. 56% of the study population is between 10-19 years of age and 24% between 20-19 years. Practice of ear piercing in and younger age group may be attributed to increased incidence in younger persons. Also younger people usually wish to remove their scar marks and seek medical help often. Majority of our patients developed keloids following ear piercing. Ear lobule piercing as well as second stud piercing also led to keloid formation. Majority of ear piercing was done by gold workers in jewelleries using either needle or using ear piercing gun. Very few patients sought medical help for ear piercing. Following ear piercing, trauma was the second cause of keloid formation in our study. Most of them were untidy wounds with foreign bodies and caused secondary infection Of the 45 cases studied, 17 patients had some kind of wound complications after initial injury. 14 patients had wound infection following Surgery, ear piercing and trauma. 2 patients had foreign body and 1 patient had stitch granuloma. Wound infection, tension and foreign bodies in the surgical site are well known triggering factors for fibrosis and subsequent keloid formation. 10-12 Keloids tends to occur after months to ears after initial insult and tend to grow during this face without any signs of regression unlike other scars. The mean age after incidence of the keloid in

this study was 3.42. Maximum age was 10 years and a minimum time period of 1 year was set to be included in the study after the occurrence of the keloid. No definite association between age of the keloids and chance off recurrence were found, but early keloids tend to respond well to certain treatment modality such as radiation and cytotoxic drugs. 13,14 There is a clear genetic background for keloids but the exact alterations are yet to be described. 15-17 Other studies have demonstrated reduced expression of pro-apoptotic genes as well as differential expression of these genes in same keloid itself. Proapoptotic ADAM-12 gene up-regulation in the central core of the Keloids are seen. 18 These suggest an important role for programmed cell death in the progression of the disease and a genetic variability depending on the location of the sample acquisition. These observations suggest a genetic predisposition that may give us further insight into the pathophysiology of keloids. Genomic studies don't show any particular gene responsible for keloid formation. 12 of the study group persons have family history of keloids in the first degree relatives. These patient tent to have increased incidence of recurrence and keloid tentencies. 8 out of the 12 pateints had recurrence of the disease in our study that is 67% recurrence. Tendency of the patients to form keloids were also enquired such as keloid formation in BCG scars and previous traumas. History of multiple keloids in same individual is also recorded. 20% of the patients in the study showed tendency for keloid formation. Many of these patients also have family history of keloids in near relatives which also supports strong genetic back ground.

Out of 45 patients, 22 didn't undergo any modality of treatment. Few of the patients took multimodality treatment. 15 patients took multiple triamcinolone injections. 10 patients underwent excision and presented back as recurrence. Six patients used silicone products on their scars previously and one patient used laser previously.

Keloids are fibro-proliferative disorders very notorious for recurrence. By the definition of the study recurrence means any extension of the scar beyond original surgical wound and any elevation of scar from normal surrounding skin. Surgical removal alone as a therapy has an overall recurrence rates ranges from 40-100%. Adding adjuvant therapies will reduce recurrence after excision. Most commonly used adjuvant is Intralesional triamcinolone which combined with surgery have a recurrence rate of 40-50%. Giving few fractionated radiation to the post excision scar will further reduce recurrence up to 20% in the expense of higher complication rates. In our current study, recurrence rates are documented as 48.9% which is better than surgical excision alone and comparable to other adjuvants.

This is the first study published regarding the effectiveness of epidermal growth factor in reducing recurrence of keloids after excision. Advantage of using epidermal growth factor is that, it doesn't have any

potential adverse effects recorded in the study and can be a potential replacement for current therapies. However this study is limited by the low sample size as well as limited follow up period. Moreover the study is uses qualitative assessment so observer error can be there. We are currently continuing the study extending the follow up period as well as sample size, also including quantitative variable for assessing scar quality

There is a dearth of randomized controlled trials and quantitative analysis supporting the efficacy of epidermal Growth factor in preventing keloid recurrence after surgical excision. However, the subjective improvements seen in some cases are encouraging. The authors hope that this study will be a foundation for future studies and will highlight the breadth of knowledge yet to be explored by this therapy.

CONCLUSION

Keloids are an important cosmetic problem in our society and recurrence is very common whatever may be the treatment modality offered. Novel treatment involving growth factors and immunomodulators are going to be the key to the future.

This study enlighten into the possibility of using epidermal growth factors in reducing recurrence rates of keloids. Though the study is limited with small sample size and short follow up period, this study can be used as a step stone to large randomized controlled trials regarding feasibility of using epidermal growth factor in treating resistant keloids in the future.

ACKNOWLEDGEMENTS

I am grateful to Almighty for the help showered upon me for this project. I express my sincere gratitude to my beloved teacher Dr. Ajayakumar K Professor of Department of Plastic and Reconstructive Surgery for his kind guidance, inspiration and support throughout the study. I am extremely thankful to Dr I. P Yadev sir Associate professor Department of General Surgery for analysing the study and guiding the formatting. I am thankful to my beloved Head of the Department, Dr. Aniraj R who inspired me to the core. I am thankful to all the Faculties, Post Graduates, and other staff of Department of Plastic and Reconstructive Surgery for the great assistance and help given, without which this study would not have materialized. Above all, I am indebted to all Patients, and their caretakers and operation theatre staff who participated in this study with their kind cooperation. I am thankful to my parents and wife who have been my pillars of strength throughout my life.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

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Cite this article as: Joseph A, Kochunarayanan A, Varghese F, Kalesh Sadasivan. Recurrence of keloids after application of epidermal growth factor. Int Surg J 2019;6:3341-6.