Original Article

Comparison between the Efficacy of 5% Imiquimod Cream and Intralesional Triamcinolone Acetonide in the Prevention of Recurrence of Excised Ear Keloid: A Prospective Randomized Study

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Background: Ear keloid scars represents an abnormal, exaggerated healing response after skin injury. In addition to cosmetic concern, scars may cause pain, pruritus, or contractures. Nowadays, topical therapies have increased because they are easy to use, comfortable, and non-invasive. The 5% imiquimod cream has been reported as effective to prevent the recurrence of ear keloid after surgical excision.

Objective: To evaluate the efficacy of 5% imiquimod cream in decreasing the recurrence rate of keloid after surgical excision, when compared with triamcinolone acetonide injection.

Materials and Methods: Thirty patients, which included 6.67% male and 93.33% female, enrolled in a prospective-randomized study. Sixteen patients were informed to use triamcinolone injection (10 mg/mL) and 14 patients were informed to apply 5% imiquimod cream (nightly every other day) for 12 weeks after the ear keloid was excised and the stitches removed.

Results: The 30 patients were examined of recurrence of ear keloids on their ears for 48 weeks after surgical excision. The overall mean of Vancouver Scar Scale at one year for evaluating the effectiveness of imiquimod to decrease recurrence rate when compared with triamcinolone acetonide injection showed at 6.50 and 4.25 respectively. The patient satisfaction was slightly higher in triamcinolone group. However, the two outcomes, the Vancouver Scar Scale (p=0.389) and the patient satisfaction (p=0.833), were not statistically significant. No serious local and systemic adverse event was detected in either groups of patients.

Conclusion: Treatment of surgical excision ear keloids with triamcinolone acetonide injection might be a better selection as compared to imiquimod cream for effectiveness in term of lower recurrence rate and higher patient satisfaction. A limitation of the present study is the number of the patients.

Keywords: Keloid, Imiquimod, Triamcinolone acetate, Recurrence of ear keloid

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Formation of scars is a natural response of injured tissues in wound healing processes. Scars are considered abnormal when the amount of fibrosis is excessive (i.e., hypertrophic or keloid scar)[(1)]. Keloids, in particular, can cause functional, aesthetic, and emotional issues. Recently, several therapeutic modalities have been described for treatment and scar prevention such as intralesional steroid injection, radiation therapy, silicone gel sheet, and topical medication. They were reported to be adequate to treat keloids but the mechanisms were not sufficiently explained. Surgical excision alone has shown varying degree of success and recurrence rate. The combination of perioperative non-surgical therapies is anticipated to assist the prevention of recurrences after surgical excision.

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Table 1. Vancouver Scar Scale

	Feature	Score
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pigmentation	Normal	0
	Hypo-pigmentation	1
	Mixed-pigmentation	2
	Hyper-pigmentation	3
Pliability (elasticity)	Normal	0
	Supple (flexible with minimal resistance)	1
	Yield (giving way to pressure)	2
	Firm (inflexible, not easily moved, resistant to manual pressure)	3
	Banding (rope-like tissue that blanches with extension of the scar)	4
	Contracture (permanent shortening of scar, producing deformity or distortion)	5
Height	Flat	0
	2 mm	1
	2 to 5 mm	2
	5 mm	3
Pain	None	0
	Occasional	1
	requires medication	2
Itchiness	None	0
	Occasional	1
	Requires medication	2

Five percent imiquimod cream is a topical immune response modifier. It is composed of toll-like receptor agonists that have been reported to be effective in preventing recurrences of keloids after surgical excisions. However, the number of studies is inadequate.

The present study was designed to compare the recurrence rate of ear keloids in a group of patients who received 5% imiquimod cream with another group of patients who received intralesional steroid injection. Furthermore, it is to compare patient satisfaction in the result of the treatment between the two groups and to study the adverse effects of 5% imiquimod cream.

Materials and Methods

A prospective, randomized study was conducted at Ramathibodi hospital between December 2015 and December 2016 of patients once a plastic surgeon diagnosed a stable ear keloid, and excision was requested. A keloid scar at the ear at lobule was defined clinically as scar tissue extending beyond the scar border and showing no tendency toward regression. The patient demographic data was collected, including name, age, sex, underlying diseases, family history of keloid, clinical manifestation of scars, previous surgical or medical treatment, and associated symptoms. The inclusion criteria were 1) ear keloid scars, over one-year duration without progression and did not receive any treatments within two months, 2) ear keloid scars able to be almost entirely excised and closed primarily with acceptable cosmetic result, and 3) patients aged over 18 years old. The exclusion criteria were 1) patients with contraindication for local anesthesia, 2) patients with underlying diseases such as hypertension, ischemic heart disease, or immune deficiency, and 3) patients with contraindication for imiquimod cream such as a history of allergy to imiquimod or pregnancy. Thirty keloids at the ear were excised with primary bilayer closure. The patients were divided into two groups, 16 patients in the control group were instructed to inject triamcinolone acetonide 10 mg/mL, starting one week after suture removal, until the scar flatten, while the other 14 patients in the study group were instructed to apply 5% imiquimod cream one week after suture removal nightly, everyday at the surgical area for 12 weeks. Patients were assessed with scores from the Vancouver Scar Scale at 2, 4, 8, 12, 24, 32, and 48 weeks (Table 1). The present research project had been certified by the Human Research Ethics Unit, Faculty of Medicine Ramathibodi Hospital, MURA2015/592.

Statistical analysis

The present study was a preliminary study and the sample size was taken to be approximately 15 per arm, as this was a feasible number of patients seen during the study period. Randomization was done using computerized random number generator in blocks of four.

The characteristic information of categorical data was described by chi-square test, and continuous data were described by student t-test. For efficacy between the two groups, comparison for longitudinal periods was analyzed by repeated measure analysis of variance (repeated ANOVA). The significant level was defined as p-value less than 0.05. Analyses were carried out using the Stata, version 14.1 (StataCorp LP, College Station, TX, USA) (licensed to the Section for Clinical Epidemiology and Biostatistics Ramathibodi Hospital).

Table 2. Patients result data (n=30)

Variables	Triamcinolone acetate (n=16) Mean±SD	Imiquimod (n=14) Mean±SD	p-value
Age (year)	26.9±9.41	26.9±6.44	0.99
Sex; n (%)			
Female	15 (93.75)	13 (92.86)	0.99
Male	1 (6.25)	1 (7.14)	
Vancouver Scar Scale			
Pre-operative	5.69±1.85	4.86±1.88	0.23
Post-operative 1 month	5.75±2.21	4.64±2.06	0.17
Post-operative 2 months	4.75±1.57	5.07±2.09	0.64
Post-operative 3 months	4.13±1.26	4.86±2.28	0.28
Post-operative 1 year	4.25±1.57	6.50±3.13	0.04
Follow-up time after last injection (months); median (IQR)	12 (12 to 12)	8 (6 to 10)	<0.05
Satisfaction at 1 year	7.63±1.09	7.71±1.20	0.83
Long terms results at >1 year; n (%)			
Good result	7 (43.75)	10 (71.43)	0.14
Persistent of recurrence	8 (50.00)	3 (21.43)	

SD=standard deviation; IQR=interquartile range

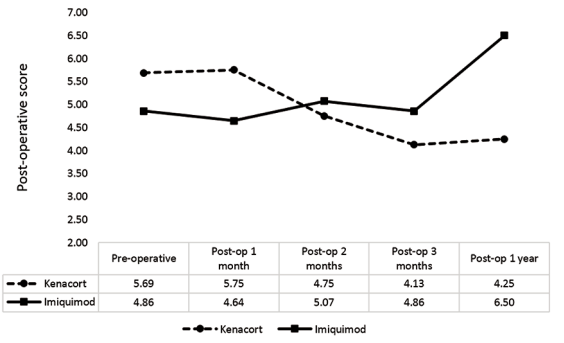

Figure 1. Overall mean scores based on the postoperative Vancouver Scar Scale for evaluating the effectiveness in preventing recurrence between the standard triamcinolone acetonide (10 mg/mL) injection and 5% imiquimod cream.

Results

Thirty patients were enrolled in the present study (Table 2). Two patients were male (6.67%), and twenty-eight patients were female (93.33%). There was only one male patient in each group. All of the lesions were keloid at the ear lobules. The mean age was 26.9 years in both the triamcinolone and the imiquimod groups. All the patients were followed up for at least one year after surgical excision and were evaluated clinically with the Vancouver Scar Scale. Good long-term result, defined as no recurrence at one year, was 43.75% in the triamcinolone group and 71.43% in the imiquimod group (no scientific significance). Recurrence of an excised keloids, defined as any indurated papule or nodule extending beyond the borders of a healed excision line, were 50% in the triamcinolone group and 21.43% in the imiquimod group. The long-term result over one year of both groups was not statistically significant (p=0.14).

Two patients complained about pruritus with the application of imiquimod cream. No severe systemic adverse effect was detected in either groups. Patients satisfaction was also evaluated by using the mean of the visual analog score. In the triamcinolone acetonide injection group and the imiquimod group, the scores were 7.62 and 7.71, respectively, which was not statistically significant (p=0.833).

Overall mean scores of post-operative Vancouver Scar Scale at 1, 2, 3 months, and 1 year were not statistically different between the two groups (p>0.05), even though there was a trend to have higher scores in the imiquimod group (Figure 1).

Discussion

Keloids at the ear lobule have an upregulation of collagen synthesis, deposition, and accumulation. Currently, the underlying regulatory mechanisms responsible for this excessive repair are still under investigation. Both profibrotic cytokines such as transforming growth factor-β1 (TGF-β1) as well as a lack of programmed cell death, or apoptosis, of

activated fibroblasts secreting extracellular matrix components, have been implicated in excessive scarring[2].

Surgical excision of keloids alone has a reported recurrence rate of between 45% and 100%. Adjuvant therapies for keloids include steroid injection, radiation, cryotherapy, laser, and antitumor or immunosuppressive agents. In general, the first line of adjuvant therapy is intralesional corticosteroid injections. Triamcinolone acetonide at 10 mg/mL is generally tried initially, and if no response occurred, a 40 mg/mL concentration is attempted. Injection into the thick scar is often painful and associated with risk of infiltration into the surrounding healthy tissue. Early, rapidly proliferating lesions respond best to steroid injections whereas slow growing or mature keloids respond poorly. However, the rate of recurrence is varied among 14% to 40% after surgical excision and combined corticosteroid injections plus topical steroid application[3]. Similarly, the auricular keloids could have recurrence rate of 5% to 20% in excision and post-operative corticosteroid injection[4]. The various results of treatment of steroid injection are due to different anatomical locations, protocol of injections and also contour of the keloids which determines who are responders or non-responders[5].

Many researchers have paid more attention on the immunoregulation of collagen production and deposition. The immune mediators studied are the interferons (IFNs), which are produced by activated T cells and known to be antifibrotic. The previous study showed that the IFN increased collagen breakdown[6] and, in addition, collagenase levels were increased from their subnormal levels in the keloid studied[1,2]. These findings correlate with the clinical decrease in size of the keloid studied. Berman and Kaufman[2] also showed that patients with keloids demonstrated markedly reduced levels of IFN production by peripheral blood mononuclear cells. Berman and Flores demonstrated a reduction in the postoperative recurrence rate of keloids treated with IFN alfa-2b immediately after excision[1]. Other studies also demonstrated antimitotic drugs, 5-FU, bleomycin, mitomycin, could inhibit fibroblast proliferation and promote apoptosis but still limited in use due to the adverse affect and cessation of the treatments led to recurrence[7].

The 5% imiquimod cream, approved by the U.S. Food and Drug Administration for the treatment of anogenital warts, actinic keratosis, and superficial basal cell carcinoma[6], is an immunomodulator that induces the synthesis many of inflammatory cytokines especially IFN- α[8]. The action of these cytokines is mainly associated with local effects and an up-regulation of tumor suppressor gene, which promote apoptosis[9], reduce the synthesis of collagen type I, III, and promote collagen activity. A pilot study examining the use of 5% imiquimod cream on post-surgical wounds in keloid-forming patients found lower recurrence rates of keloids than reported in the literature[10].

In the present study, all of the keloids were lesions at the ear with low tension effect after surgical excision. Follow-up periods ranged from 6 to 12 months with an average of 10.1 months. From the present result, five patients (31.25%) in the triamcinolone group and four patients (28.57%) in the imiquimod group were completely healed. Although the statistical analysis showed no statistically significant difference between the two groups about the effectiveness to prevent the recurrence of keloid, there were four patients (28.57%) in the study group that had a recurrence and required further surgical excision. They were switched to use the triamcinolone acetonide injection. Furthermore, all lesions were located at the helical rim. However, the pre-operative size of keloid at the helical rim might limit the excision due to cosmetic concern, which related to the recurrence rate. The earliest height of scar from the Vancouver Scar Scale, which is more than 2 millimeters, might demonstrate the importance of the residual volume of keloids, which could also associate with the recurrence rate when the 5% imiquimod cream is applied. Application of the 5% imiquimod cream was well tolerated with few side effects. Only two patients complained about the pruritic symptom at the area of application. If irritation developed, the application of the medicine would be adjusted until it resolves.

The limitation for the present study might affect the results. Further study to be conducted should include more patients to avert statistical errors.

Conclusion

Treatment of post-surgical excision of keloid scar by applying 5% imiquimod cream was well tolerated without serious adverse events. This topical agent could be considered to decrease the recurrence rate of keloids in post-operative keloid excision. Nevertheless, there is no marginal exclusivity between the 5% imiquimod cream and the regular triamcinolone acetonide injection in terms of the effectiveness in preventing the recurrence of excised keloids, cost, and patients satisfaction with no

statistical difference.

The authors have indicated no significant interest with the commercial supporters.

What is already known on this topic?

Keloids, the abnormal scars after injuries, are difficult to treat in terms of prevention of recurrence. Surgical excision of keloid has a high rate of recurrence, however, it is still the standard treatment in specific keloids that are big with irritating symptoms, and it always requires post-operative treatment such as steroid injection or pressure garment.

What this study adds?

An option of post-excision treatment is available by using 5% imiquimod cream. Even though the recurrence rate is slightly higher compared to the intralesional triamcinolone, it causes less pain and is usable in patients with contraindication to steroid injection.

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Conflicts of interest

The authors declare no conflict of interest.

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