The Efficacy of 5% Imiquimod Cream in the Prevention of Recurrence of Excised Keloids

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Objective: *To evaluate the efficacy of 5% imiquimod cream in the prevention of recurrence of excised keloids.*
Material and Method: *The patients with keloids that had occurred over 1 year and could be excised and primary sutured were enrolled in the study. Imiquimod 5% cream was applied to the scar 7 days after stitches removal. The patients were follow-up for recurrence and drug side effect at 4, 6, 8, 16, and 24 weeks*
Results: *Forty-five patients enrolled to the study but only 35 patients finished the study. The keloids were at the pinnas in 22 patients, at the backs or shoulders in 7 patients, and at chest walls or necks in 6 patients. Imiquimod 5% cream was applied on the wound area 2 weeks after the operation, at alternate night for 8 weeks. The follow-up period ranged from 6 to 9 months. Ten of the treated keloids recurred (28.6% recurrent rate). The lesion at the pinna had the lowest recurrent rate (2.9% recurrent of the total patients). The highest recurrent rate occurred at the chest wall or neck (83.3% recurrent of the chest wall or neck or 14.3% of the total patients). Side effects were found in thirteen patients (37.1%). These were abrasions of the skin around the wound areas in ten patients and hyperpigmentation of the skin around the wounds in three patients.*
Conclusion: *Imiquimod 5% cream could effectively prevent recurrence of the excised keloids, especially in the area that had less tension such as pinna.*

Keywords: *Keloid, Imiquimod, Scar*

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Keloid is one of the common skin lesions in Thailand and in dark skinned people[1]. It causes physical and mental discomforts. Steroid injection is the mainstay of keloid therapy, especially for small lesions. For larger ones, surgical excision by scalpel or laser is a common management[2]. This should be followed by adjuvant therapy such as steroid injection, radiation, or pressure to prevent recurrence[3,4]. Recently, imiquimod, an immune response modifier, has been reported as an adjuvant therapy after surgical excision of keloid on a limited number of patients[5-7]. In the present study, the authors evaluated the effectiveness of topical imiquimod to prevention the recurrence, after excision, of a keloidal scar in the treated area, a with and without tension.

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Material and Method

The patients who had lesions diagnosed by plastic surgeons as keloid scar and requested excision of the lesions were informed by the authors about the research protocol. The inclusion criteria of the patients were as follows: 1) keloid scars, over one year duration and did not receive any treatment within 2 months; 2) keloid scar able to be totally excised and closed primarily with acceptable cosmetic result; 3) patients aged over 18 years. Patients younger than 18 years old should receive permission from their parents before enrolled in the present study.

The exclusion criteria were: 1) patients with contraindication for local anesthesia, hypertension, ischemic heart disease, pregnancy, or immune deficiency; 2) patients with a history of allergy to imiquimod.

All the lesions were excised by one of the authors. Local anesthesia (1% lidocaine with adrenalin) was used. The incision was sutured in two layers. Skin sutures were taken out on the seventh day after the

operation. The patients were instructed to apply 5% imiquimod cream to the wound area at alternate nights for eight weeks starting from one week after the wounds were stitched off. Patients were assessed at 4, 6, 8, 16, 24 weeks after surgery for erythema, pain, pruritus, erosion, and hyperpigmentation at the application site, and for systemic symptoms such as fever, chills, myalgias, and headache as well. Although the final assessments were at 24 weeks, several patients also came for further follow up.

Results

There were 45 patients enrolled in the present study but only 35 patients were completely studied from 1 August 2005 to 30 April 2006. Thirty-two patients were female and three were male. The patients' age ranged from 10 to 48 years. Twenty-two keloid lesions were at the ear lobules, seven lesions at the backs or shoulders, and six lesions at chest walls or necks.

The follow-up periods ranged from 6 to 9 months. Ten of the treated keloid lesions recurred (28.6% recurrent rate). These were one at the ear lobe (4.5% recurrent rate of the ear lobe site or 2.9% recurrent rate of total cases), four lesions at backs or shoulders (57.1% recurrent rate of the back or shoulder area or 11.4% recurrent rate of total cases), and five lesions at chest walls or necks (83.3% recurrent rate of the chest wall or neck, or 14.3% from total cases).

Thirteen patients (37.1%) had side effects from the application of imiquimod. These were abrasion of skin around the wound area in ten patients and hyperpigmentation of the skin around the wound in three patients. In the group of abrasion, seven lesions had small spots of abrasion and three had abrasions at almost the entire wound area. One of the patients in the abrasion group had wound disruption and needed re-suturing.

These side effects were resolved after the drug was withdrawn. The patients could re-apply the drug after 2 weeks.

Discussion

Keloid is one of the common skin problems that surgeons and general practitioners usually encounter. The pathogenesis of keloids includes tension, excessive production of collagen and extracellular matrix, increased level of types 1and 2 of TGF-□, lower rates of apoptosis of keloid fibroblast, tissue hypoxia and abnormal immune mechanism[1,2].

Steroid injections are often used for the initial treatment of keloid and for post operative adjunctive treatment. The adverse effects of steroid infection are depigmentation, atrophy of the dermis and fat, and telangiectasia. Pain during injection is a major draw back for this treatment modality especially in children[2,3].

Pressure[8] and silicone gel sheath[9,10] were used for prevention of recurrence of keloids with varying results (55% cure rate for pressure, 66.67% for silicone gel sheath).

Seventy to ninety percent recurrent-free rates were reported using radiation therapy for keloid prevention after excision[4,11]. Hyperpigmentation and uncertain chance of malignant change are disadvantages of this treatment modality.

Interferon interferes with fibroblasts' ability to synthesize collagen. Injection of interferon - α-2b into the keloid excised wound was used. The recurrent rates ranged from 18.7-54%[12,13].

Imiquimod, an immune response modifier that indirectly acts to stimulate innate and cell mediated immune pathways, enhances the body's natural ability to heal. Imiquimod induces and activates natural killer cells, macrophages and Langerhans cells and also induces the local synthesis and release of cytokines, including IFN-α, IFN-γ, tumor necrosis factor-2 and

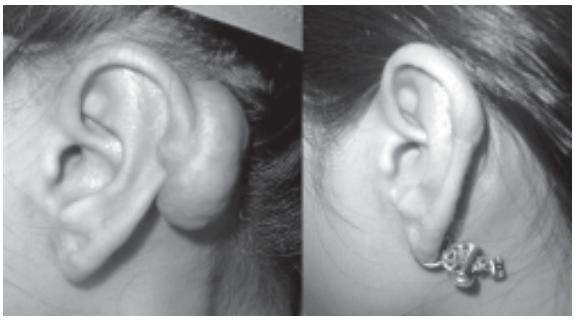

Fig. 1 A keloid at the pinna and the result at 9 months

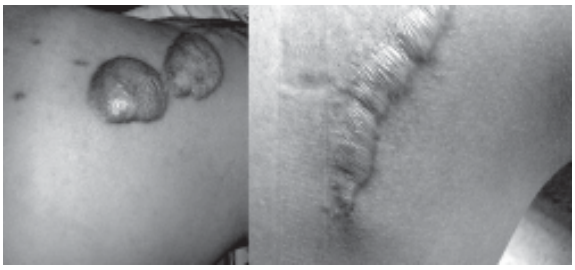

Fig. 2 A keloid at the shoulder and the result at 6 months with recurrence

Table 1. Demographic data of the patients with keloidal scar

Case No.	Age	Sex	Site of lesion	Duration (years)	Follow up, period (month)	Recurrence
1	31	female	chest wall	5	9	+
2	21	female	Rt.pinna	4	9	-
3	23	female	Rt.pinna	3	9	-
4	21	female	Rt.pinna	3	9	-
5	22	female	neck	3	9	-
6	24	male	Lt.pinna	2	9	-
7	47	female	Rt.pinna	5	9	-
8	23	male	Lt.pinna	2	9	-
9	24	female	Lt.pinna	2	9	-
10	25	female	Rt.pinna	2	8	-
11	21	female	Lt.pinna	1	8	-
12	25	female	Lt.pinna	2	8	-
13	23	female	Rt.pinna	2	8	-
14	15	female	Lt.pinna	2	8	+
15	33	female	Rt.shoulder	10	8	+
16	25	female	Rt.pinna	1	8	-
17	23	female	Lt.pinna	1	8	-
18	27	female	back	3	8	-
19	48	female	chest wall	30	8	+
20	20	female	Lt.shoulder	5	8	+
21	14	female	Rt.pinna	3	8	-
22	16	female	Lt.pinna	2	8	-
23	22	female	Lt.pinna	1	8	-
24	32	female	chest wall	6	7	+
25	30	female	Rt.shoulder	5	7	+
26	23	female	Lt.shoulder	5	7	+
27	23	female	Rt.pinna	2	7	-
28	23	female	Lt.pinna	2	7	-
29	20	female	Lt.pinna	1	7	-
30	15	female	Lt.pinna	1	7	-
31	20	female	Rt.pinna	1	7	-
32	22	female	Rt.shoulder	5	7	-
33	25	female	chest wall	4	6	+
34	35	female	back	10	6	-
35	10	male	chest wall	2	6	+

interleukins -1, -6, -8 and -12 when topically applied[5-7]. The expression of genes associated with apoptosis was also significantly altered in keloidal tissue treated with imiquimod 5% cream[14]. It has also been used as an antiviral or antitumor agent with successful results[6,7]. Kaufman and Berman [5] reported the effect of topical application of imiquimod 5% cream after surgical excision of 13 keloids from 12 patients. At 24 weeks, no recurrence of keloids was noted among the 11 keloids of 10 patients who completed the study. In their study, hyperpigmentation occurred in 60% of the patients. This hyperpigmentation might be caused by early application of imiquimod cream. There were a few reports on the effect of topical imiquimod after keloid excision[5,6,14].

In the present study, the authors recruited only keloid lesions in various regions of the body. Follow-up periods ranged from 6 to 9 months with an average of 7.9 months. Ten from 35 patients had some degree of recurrence (raised and thick scar) (28.6% of total recurrent rate). According to the regions of the body, the ear lobe had the lowest recurrent rate (1 from 22, 4.5% recurrent rate); chest wall region had the highest recurrent rate (5 from 6 lesions, 83.3% recurrent rate).

The neck and shoulder area had a 57.1% recurrent rate.

These results might suggest that imiquimod reduced recurrence better in less tension wound area.

Thirteen patients had side effects from local application of imiquimod. These included abrasion of skin around wound edge in 10 patients, and hyperpigmentation of the skin around the scar in three patients. The abrasion healed after drug withdrawal for a few days. The drug could be reapplied without any complication.

If the irritation of the skin develops, application should be adjusted to longer interval of application. It can resume to the same protocol when the irritation is resolved. No systemic side effects were observed in the present study.

Longer follow up periods should be studied for recurrence of keloids and whether re-application of imiquimod could treat the newly formed keloids.

Conclusion

Topical application of 5% imiquimod for prevention of keloid recurrence yielded a 28.6% recurrent rate on an average of 7.91 months of the follow-up period. At less tension areas (ear lobe), the recurrent rate was 4.5%. This therapy might be useful for the prevention of keloid recurrence after surgical excision.

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ประสิทธิภาพของ 5% อิมมิคิวม๊อดครีมในการป้องกันการกลับเป็นซ้ำในแผลเป็นคีลอยด์ที่ได้รับการตัดออก

อภิรักษ์ ช่วงสุวนิช, สุริยา กุลจิตติสำราญ

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของ 5% อิมมิคิวม๊อดครีมในการป้องกันการกลับเป็นซ้ำในแผลเป็นคีลอยด์ที่ได้รับการตัดออก*

วัสดุและวิธีการ: *ผู้ป่วยที่เข้าร่วมโครงการต้องมีแผลคีลอยด์นานเกินกว่า 1 ปี และสามารถตัดออกแล้วเย็บปิดบาดแผลได้ หลังจากตัดไหม 7 วัน ให้ทายา 5% อิมมิคิวม๊อดครีมรอบบริเวณแผลเป็นก่อนนอนวันเว้นวัน เป็นเวลา 8 สัปดาห์ ผู้ป่วยได้รับการติดตามผลของการใช้ยาที่ 4, 6, 8, 16, 24 สัปดาห์*

ผลการศึกษา: *มีผู้ป่วยที่มีแผลเป็นคีลอยด์ 45 ราย ได้รับการตัดคีลอยด์ระหว่าง 1 สิงหาคม พ.ศ. 2548 ถึง 30 เมษายน พ.ศ. 2549 แต่มีเพียง 35 รายที่สามารถติดตามผลได้ตามกำหนด แบ่งเป็นที่ใบหู 22 ราย เป็นที่ไหล่หรือหลัง 7 ราย และ 6 ราย เป็นที่หน้าอกหรือคอ มีการติดตามนาน 6-9 เดือน ผู้ป่วย 10 รายเกิดกลับเป็นใหม่ของแผลเป็นคีลอยด์ (อัตราเป็นซ้ำ 28.6%) พบผลข้างเคียงจากการใช้ยาในผู้ป่วย 13 ราย (37.1%) ผลข้างเคียงที่พบคือมีการถลอกของผิวหนังรอยแผลในผู้ป่วย 10 ราย เกิดเป็นรอยคล้ำรอยแผลในผู้ป่วย 3 ราย*

สรุป: *ยา 5% อิมมิคิวม๊อด อาจจะช่วยป้องกันการกลับเป็นซ้ำในแผลคีลอยด์ที่ได้รับการผ่าตัด โดยเฉพาะในบริเวณที่มีความตึงของแผลเป็นไม่มาก เช่น ที่บริเวณติ่งหู*