Could 5-Fluorouracil or Triamcinolone Be an Effective Treatment Option for Keloid After Surgical Excision? A Meta-Analysis

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Purpose: There is no universally accepted treatment regimen to decrease the recurrence rate of keloid formation after its removal, although many treatment options have been suggested. The purpose of this study was to investigate treatment options to prevent keloid recurrence after surgical excision.

Materials and Methods: A systematic literature review and meta-analysis was performed using the Medline, Embase, and Cochrane databases. Predictor variables were 5-fluorouracil (5-FU) or triamcinolone adjuvant therapy, and the outcome variable was keloid recurrence rate. The Newcastle-Ottawa scale was used to assess the quality of the studies and the Cochrane risk-of-bias tool was used. Publication bias was evaluated using a funnel plot.

Results: There were 1,224 publications identified; after screening, 5 were selected for review (1 retrospective cohort, 3 prospective cohorts, and 1 randomized controlled trial). The mean level of keloid recurrence was statistically lower in patients who received 5-FU compared with those who did not (control group; risk ratio, 0.18; 95% confidence interval [CI], 0.04 to 0.75). Triamcinolone was ineffective in lowering the keloid recurrence (risk difference, 0.06; 95% CI, −0.16 to 0.28).

Conclusion: 5-FU can be considered an effective treatment to decrease keloid recurrence after surgical excision, although further research, including a randomized controlled trial, is required.

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Keloid and hypertrophic scars are undesirable outcomes of wound healing caused by deep wounds that extend into the dermis. Hypertrophic scars occur along the border of the original wound, whereas keloid tissue is present beyond the original wound and is accompanied by wound elevation.[1] Keloids and hypertrophic scars are believed to be the outcome of excessive dermal fibrosis and cutaneous scarring and are caused by disruption of the regulation of cellularity during the wound-healing process.[2,3] Keloids are physically disfiguring and cause mental stress, severe pain, and an itching sensation.[4]

The first treatment approach is usually compression therapy using silicone-based products. A minimum of 3 to 6 months of compression therapy is needed; if there is no improvement, then an injection treatment should be considered as a secondary treatment option.[1] However, these treatments are the general consensus, and treatment sequences can be changed according to the preference of the surgeon.

Corticosteroids are most commonly used as injection treatment in the early stage of the maturation phase, but in some cases 5-fluorouracil (5-FU), bleomycin, or verapamil can be considered.[5] Nonreactive refractory keloids remaining after these noninvasive treatments should be considered for surgical treatment. Because keloids have a high recurrence rate after surgical excision, adjuvant therapy, such as corticosteroid, 5-FU, radiotherapy, or cryotherapy, is required after surgical excision of the keloid.[6,7]

The primary management of keloids has been extensively studied, but management after keloid excision

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has received less attention. In addition, there is no standard treatment option after keloid excision has been established. Management strategies after keloid excision can involve treatment with corticosteroids, radiotherapy, 5-FU, bleomycin, interferon, botulinum toxin, or simple compression therapy.[8-16]

The purpose of this study was to evaluate treatment results of 5-FU and triamcinolone and identify the more effective and appropriate management approaches. Various studies were analyzed by meta-analysis to compare the recurrence rate according to 5-FU or triamcinolone adjuvant therapy. The authors hypothesized that 5-FU or triamcinolone adjuvant therapy, 2 widely used treatments, would be substantially more effective than other treatments.

Materials and Methods

STUDY DESIGN AND SAMPLE

To address the research purpose, the authors designed and implemented a systematic literature review and meta-analysis. The authors independently searched for eligible articles using the Medline, Embase, and Cochrane databases for all studies published until June 2015. The following inclusion criteria were used: *1)* a full-length original article that provided sufficient data to enable evaluation of the impact of treatment modality on keloid recurrence, *2)* prospective or retrospective trials, and *3)* existence of a treatment modality after the excision of the keloid(s). Studies were excluded if they *1)* had incomplete or interim data, *2)* were carried out in vitro, *3)* were in languages other than English, *4)* lacked information regarding recurrence, and *5)* described fewer than 10 cases because these articles were regarded as case series rather than trials or cohort studies.

STUDY VARIABLES

Postoperative treatment options using 5-FU and triamcinolone were included as primary predictor variables and postoperative recurrence rate of keloid was included as an outcome variable.

DATA COLLECTION METHODS

The present meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[17] The following search formula was used for Medline: *keloid* AND ([*fluorouracil* OR *antitumor* OR *antimitotic* OR *mitomycin* OR *bleomycin*] OR [*triamcinolone* OR *steroid* OR *corticosteroid* OR *injection**] OR [*silicone* OR *silastic* OR *sheet* OR *compression* OR *sheeting* OR *pressure*] OR [*radiation* OR *irradiation* OR *x-ray* OR *gamma* OR *brachytherapy* OR *radiotherapy*]). Similar search words were used for the other databases.

DATA ANALYSIS

The ratio of recurrence in the experimental group was obtained by dividing the number of recurrent lesions by the total number of lesions in the study. The proportion of recurrence in the control group was calculated using the same method. Then, the standard error of the proportion was calculated for each clinical outcome measurement. The mean ± standard deviation was determined for each treatment (percentage improved or percentage without recurrence depending on the measurement reported), which included all separate outcome measurements. Then, the 95% confidence interval (CI) was computed for each therapy. The mean ± standard deviation of all treatment means was computed.

The Cochrane Review Manager (RevMan 5.3, The Cochrane Collaboration, Oxford, UK) also was used to analyze and graphically display the meta-analysis data. Relative risk with 95% CI for treatment outcome was calculated. The heterogeneity for each study was assessed using the I^2 test. Forest plots were constructed to illustrate the effect of the size of the studies and funnel plots were used to ascertain evidence of publication bias.

Results

STUDY SEARCH

There were 1,224 publications identified that potentially met the search criteria. The initial screening process consisted of a title and abstract review and 841 studies were excluded because they did not meet the inclusion criteria. There were 281 duplicate studies that were excluded. A total of 102 articles were reviewed for eligibility by accessing the full text, and 5 published studies were analyzed, which included 301 eligible patients (Fig 1, Table 1).[16,18-21] Q3

EFFICACY OF 5-FU AND TRIAMCINOLONE

The 5 studies were divided into 2 subgroups (Table 2). The first subgroup involving patients treated with 5-FU contained 2 studies. A fixed-model meta-analysis of these 2 studies involving 107 patients yielded a pooled relative risk for recurrence of 0.18 (95% CI, 0.04 to 0.75; $P = .02$; Fig 2) with low heterogeneity ($I^2 = 0\%$). Treatment with 5-FU lowered the risk of keloid recurrence by a factor greater than 5. The second subgroup was treated with triamcinolone and included 4 studies. A random-effect model meta-analysis of the 4 studies involving 254 patients yielded a pooled risk difference of 0.06 (95% CI, −0.16 to 0.28; $P > .05$) with moderate heterogeneity ($I^2 = 74\%$; Fig 3).

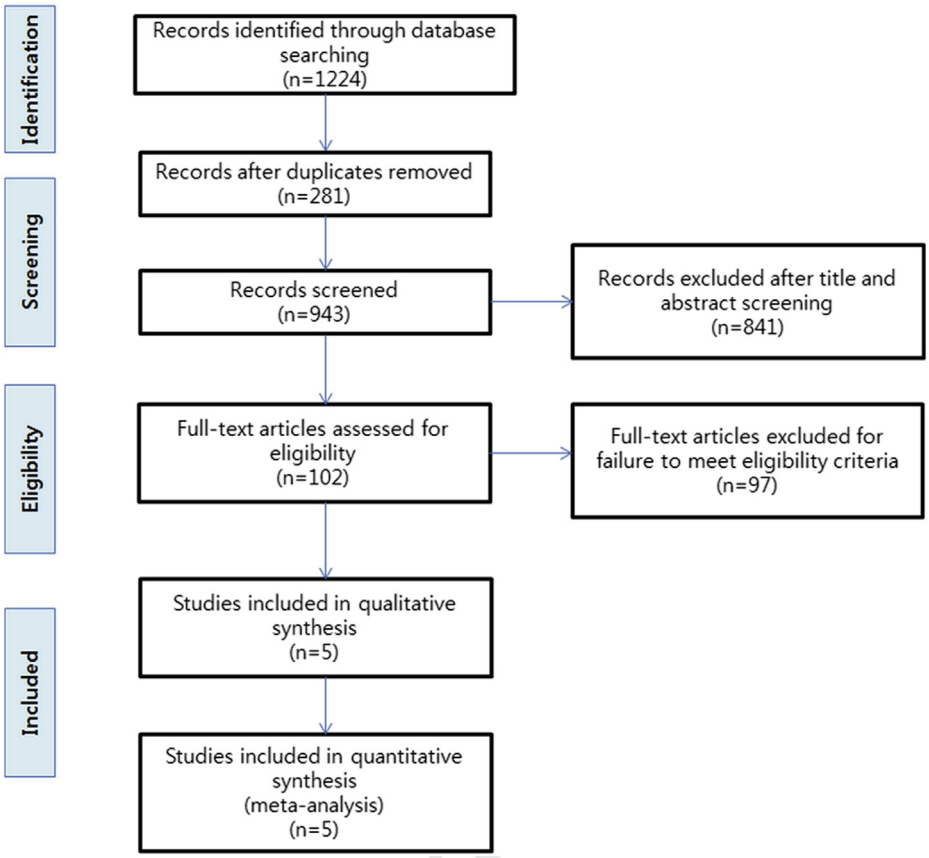

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for keloid treatment. Q4

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Table 1. CLINICAL DATA OF INCLUDED STUDIES

Study	Keloid Site	Cases (Patients), n	Gender	Age (yr)	Lesion Size (cm)	Location (Language)/Race or Ethnicity
Hatamipour et al,[21] 2011	Sternal, 19; back and abdomen, 20; deltoid, 5	47 (50)	M, 20; F, 30	22-45	2.0-6.0	Iran (English)/all Iranian
Berman and Flores,[19] 1997	Earlobe, 99; ear helix, 7; back, 1; chest, 2; extremity, 1; neck, 3; others in head, 11	124 (74)	M, 8; F, 66	8-61	0.5-15	United States (English)
Davidson et al,[20] 2006	Ear, 10; face/scalp, 8; chest, 7; extremity, 6; abdomen, 4; neck, 4	39 (34)	NA	18-62 (mean, 30.1)	NA	United States (English) /African, 21; Caucasian, 13; Hispanic, 4; Asian, 1
Khare and Patil,[18] 2012	Earlobe, all	60 (56)	M, 0; F, 56	14-56	1.2-4.8 (mean, 2.6)	India (English)
Sclafani et al,[16] 1996	Earlobe, all	31 (31)	M, 6; F, 25	mean, 28.1	mean, 2.5	United States (English) /black, 20; Hispanic, 10; white, 1

Abbreviations: F, female; M, male; NA, not available. Q5

Shin and Kim. 5-FU Versus Triamcinolone Against Keloids. J Oral Maxillofac Surg 2015.

Table 2. SUMMARY CHARACTERISTICS OF INCLUDED STUDIES

Intervention	Study	Keloid Site	Study Type	Quality Score*	Risk Ratio	Mantel-Haenszel Method, 95% CI	Weight (%)	Follow-Up (mo)
5-FU	Khare and Patil,[18] 2012	Earlobe	Prospective study	7	0.19	0.02-1.52	43.9	22
	Hatamipour et al,[21] 2011	Body trunk	RCT	Low risk†	0.16	0.02-1.25	56.1	12
Triamcinolone	Berman and Flores,[19] 1997	Earlobe, whole body	Retrospective cohort study	8	0.16	−0.01 to 0.33	28.8	47
	Davidson et al,[20] 2006	NA	Randomized prospective study	7	−0.38	−0.69 to −0.08	21.0	12
	Khare and Patil,[18] 2012	Earlobe	Prospective study	8	0.18	0.02-0.34	29.7	22
	Sclafani et al,[16] 1996	Earlobe	Randomized prospective study	7	0.18	−0.14 to 0.49	20.5	30

Abbreviations: 5-FU, 5-fluorouracil; CI, confidence interval; NA, not available; RCT, randomized controlled trial.
* By the Newcastle-Ottawa scale.
† By the Cochrane risk-of-bias tool.

Shin and Kim. 5-FU Versus Triamcinolone Against Keloids. J Oral Maxillofac Surg 2015.

Treatment with triamcinolone injection had no effect on keloid recurrence.

EVALUATION OF PUBLICATION BIAS

A funnel plot of studies in which patients received 5-FU treatment showed that they were clustered near the left corner, which was attributed to the small sample. A funnel plot of studies in which patients received triamcinolone treatment showed clustering around the midline (risk ratio, 1), which suggested less asymmetry.

Discussion

As the first meta-analysis regarding management after keloid excision, the purpose of this study was to design a future study and its findings could be used to identify effective treatment methods after keloid excision among several preventive protocols. The authors hypothesized that at least 1 treatment method among several treatments would be meaningfully effective. The specific aim was to use a meta-analysis to compare keloid recurrence rate after surgical excision in patients who underwent postoperative adjuvant treatment.

The meta-analysis showed that triamcinolone had a risk difference of 0.06 (95% CI, −0.16 to 0.28; $P = .62$) with strong heterogeneity ($I^2 = 74\%$; $P < .01$). Thus, it was not shown to be effective from this result. Of the 4 studies, only 1reported a superior outcome for triamcinolone compared with other treatments.[16,18-20]

In contrast, the present meta-analyses found that 5-FU had a risk ratio of 0.18 (95% CI, 0.04 to 0.75; $P = .02$) with little heterogeneity ($I^2 = 0\%$; $P = .91$) compared with the control group.[18,21] Although the funnel plot was close to 0 as a result of the small sample, it was considered meaningful to investigate the effects of 5-FU on keloid formation.[22]

Intralesional injection of triamcinolone is one treatment for keloid that has been frequently used after

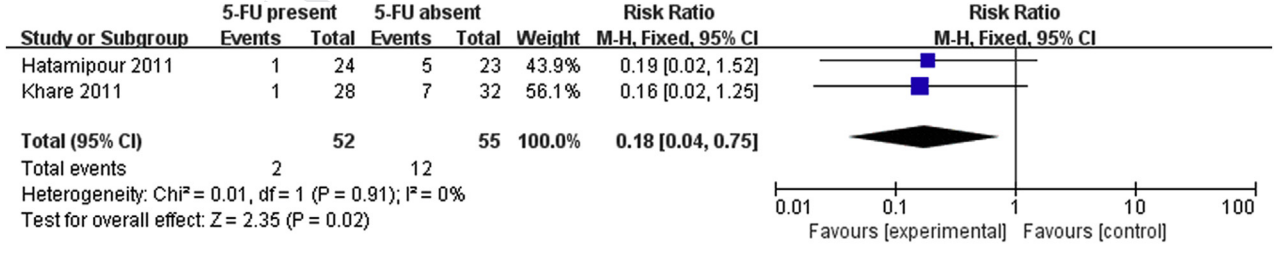

FIGURE 2. Forest plots for the evaluation of the effects of 5-FU on the recurrence of keloid. 5-FU injection showed substantial benefits concerning keloid recurrence. 5-FU, 5-fluorouracil; CI, confidence interval; M-H, Mantel-Haenszel.

Shin and Kim. 5-FU Versus Triamcinolone Against Keloids. J Oral Maxillofac Surg 2015.

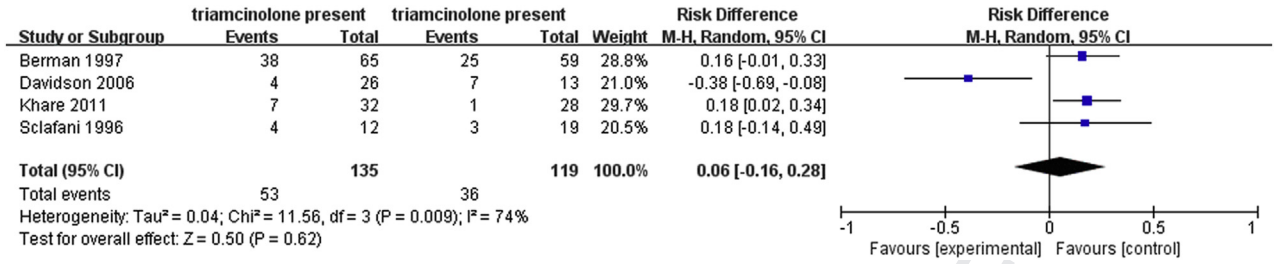

FIGURE 3. Forest plots for the evaluation of the effects of triamcinolone on the recurrence of keloid. Triamcinolone was ineffective in treating the recurrence of keloid. CI, confidence interval; M-H, Mantel-Haenszel.

Shin and Kim. 5-FU Versus Triamcinolone Against Keloids. J Oral Maxillofac Surg 2015.

keloid excision. The mechanism of triamcinolone is not completely understood. Triamcinolone is related to collagen degradation through an α-globulin collagenase inhibitor and decreased glucose-6-phosphate dehydrogenase activity.[23] It could accelerate fibroblast apoptosis by inhibiting the expression of transforming growth factor-β1.[24] The usual triamcinolone regimen involves a weekly or monthly injection for 4 to 6 months after surgical excision.[25,26] Many studies have reported good results after triamcinolone injection,[25,27] and triamcinolone is widely recognized as the main treatment for keloids. Although in rare cases skin atrophy, purpura, or dyspigmentation can occur, triamcinolone has advantages, such as cost effectiveness and low morbidity.[28-30]

However, most studies have been retrospective or noncontrolled trials. Comparative studies with other treatment groups were the only studies examined in the present study.[16,18-20]

5-FU is a pyrimidine analog with antimetabolic activity involving an inhibitory effect on human fibroblasts.[31] This drug could inhibit the proliferation and differentiation of myofibroblasts.[32] 5-FU is usually used in the form of an intralesional injection for the treatment of keloids together with triamcinolone; its excellent treatment effects have been confirmed in several previous studies.[33,34] However, there are potential serious side effects associated with 5-FU that include local erythema, pain, hyperpigmentation, ulceration, a burning sensation, and sloughing.[33,35] Many approaches have been designed to prevent these side effects. The most frequently used method is a cocktail therapy that involves mixing 5-FU with other drugs to prevent these side effects and to treat keloids effectively. Several studies have found that a combination of 5-FU and triamcinolone can achieve superior results to 5-FU or triamcinolone alone.[36-38] In addition, 1 study reported that a superior therapeutic effect could be achieved using a combination of botulinum toxin and 5-FU.[9] Therefore, although 5-FU showed good results in the treatment of keloids in this meta-analysis, further research is required to decrease its side effects and to evaluate its efficacy in combination with other drugs.

Management of keloids after surgical excision has not been previously discussed until the present meta-analysis involving 5 studies. 5-FU was found to be a considerably effective treatment for keloids. Most studies have reported an injection dose of 5-FU 50 to 150 mg at the excision margin and wound bed after keloid excision, with some differences among studies. However, triamcinolone, which is recognized as the main treatment for keloid, has not achieved better results than other treatments.

5-FU and triamcinolone inhibit exacerbated inflammatory and proliferative processes that commonly occur in keloid. In particular, excessive formation of growth factors and cytokines in the keloid lead to increased cell proliferation and extracellular matrix. 5-FU and triamcinolone restrict keloid formation by inhibiting these processes.[39] Identifying the differences between each effect of 5-FU and triamcinolone will contribute to developing more effective treatments for keloid.

The present meta-analysis had some limitations that should be acknowledged. Although the analysis included 4 prospective controlled trials and 1 retrospective study, the number of articles, sample size, and description of methodologic details were insufficient, follow-up duration differed among studies, and there were no long-term follow-up studies.

Despite these limitations, the authors believe that the present study, as the first meta-analysis of the management of keloid excision, will provide the motivation and basis for the design of a future study. Well-designed future clinical trials should overcome the present limitations and provide additional clinical support for the present findings.

In conclusion, although a large-scale randomized controlled study involving long-term follow-up is needed, 5-FU seems to be as effective as triamcinolone when used as the main treatment for keloids.

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