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ORIGINAL ARTICLE

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The combined application of bleomycin and triamcinolone for the treatment of keloids and hypertrophic scars: An effective therapy for treating refractory keloids and hypertrophic scars

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Abstract

Background: Keloids and hypertrophic scars frustrate patients by the deformity of appearance and organ dysfunction. Many modalities had been tried in clinic practice, but the results are unsatisfied.

Objective: We retrospectively analysed the combined application of bleomycin and triamcinolone for the treatment of keloids and hypertrophic scars.

Methods: The combination of bleomycin and triamcin acetonide was applied to the treatment of keloids and hypertrophic scars, 86 cases accepted the treatment. Follow-up 2–5 years after treatment.

Results: (1) The pain of scars and itching symptoms have basically subsided through treatment. (2) After drug injection treatment, the keloid began to shrink, some of the keloids disappeared. (3) Small keloids did not recur after treatment. Large keloids had local recurrence after treatment. When further treatment was given, the recurrence disappeared.

Conclusion: The combined application of bleomycin and triamcin acetonide can effectively cure keloids and hypertrophic scars.

KEYWORDS
bleomycin, hypertrophic scars, keloid, triamcinolone acetonide

1 | INTRODUCTION

Keloids are a type of scar that has an enlarged range that significantly exceeds the original lesion, accompanied by clinical symptoms such as obvious pain and unstoppable itching. At present, the clinical treatment of keloids includes surgical resection, radiation therapy, hormone injection therapy, laser treatment and cryotherapy. However, the effect of these treatments is not ideal, and the recurrence rate of keloids is still high.[1]

Over the years, we have carried out a series of exploratory research on keloid treatment, and explored a set of effective treatment methods for keloids, that is, drug treatment + surgical treatment + laser treatment. Pharmacotherapy consists mainly of the use of bleomycin and triamcinolone acetonide.

Bleomycin is an antitumor drug that effectively disrupts DNA synthesis in proliferating cells. It is clinically used for the treatment of malignant tumors, hemangiomas and other diseases.Triamcinolone acetonide is a corticosteroid drug that is clinically used in the treatment of arthritis, tenosynovitis, scars, etc.

Clinically, we have applied the combination of bleomycin and triamcin acetonide to the treatment of keloids and achieved good clinical results. After treatment, the pain and itching symptoms of keloids

basically disappeared, the hyperplasia of keloids was effectively suppressed, and the volume of keloids shrank to varying degrees or completely subsided. Below we conduct a retrospective analysis of past cases.

2 | MATERIALS AND METHODS

Cases: From June 2012 to August 2020, a total of 86 patients with keloids were treated. Age from 7 to 72 years. There were 35 males and 51 females.

Location of keloids distribution and size: 18 cases of mandibular margin and masseter muscle area, 21 cases of ear, 23 cases of chest, 13 cases of shoulder, eight cases of back, three cases of perineum. Scar size: from 0.6 cm × 0.6 cm to a huge keloid on the chest and back and perineum. Area 0–16 cm^2 47 cases, 16–49 cm^2 25 cases, 49 cm^2 or more 14 cases.

2.1 | Medications

Bleomycin (produced by Freycifers Pharmaceuticals Co., Ltd., 15,000 units/branch). With normal saline, the concentration of bleomycin is 0.05 million units / mL. Triamcinolone acetonide (Zhejiang Xianju Pharmaceutical Factory production, 50 mg / 5 mL). With normal saline with a solution, Triamcinolone acetonide concentration is 5 mg/mL.

Injection method: Inject the drug into the scar with a 1-mL syringe. Bleomycin is used in 0.05 million units/cm^2 and triamcinolone acetonide is 5 mg/cm^2. When injecting the drug, the base of the keloid should be covered so that bleomycin can effectively destroy the blood supply from the base of the keloid to inhibit the growth of the keloid and promote its atrophy.

The depth of administration of bleomycin is not too shallow, and the drug concentration is not too thick, otherwise it is easy to cause keloid ulceration. The concentration of triamcinolone acetonide is not too thick; otherwise it is easy to cause uneven regression of scars and bumps on the surface.

When injecting drugs, the drug is injected in a radial dispersal manner, and the spacing between the drug injections is less than 0.3 cm, so that the drug is evenly distributed in keloids as much as possible.

Interval of administration: The interval of treatment is determined according to the state of scar hyperplasia and the size of the scar. If the scar is dark red, full, and shiny on the surface, the scar is relatively active, and the interval between dosing is 2 weeks. If the scar is slightly dark red and has a skin texture on the surface, it can be spaced for 4 weeks. Smaller keloids are generally spaced 4 weeks apart. Due to the limitation of the dosage of the drug, the treatment of larger keloids cannot completely cover all the keloids in one injection. The drug can be taken for 3 consecutive days so that the keloids can be completely covered, and the treatment can be injected again after 3–4 weeks.

Generally, the interval between initial sessions is short, and the interval between later stages is long. When skin wrinkles appear on the surface of the keloid, the interval between dosing is 1 month. The interval between doses is not fixed and depends on the change of the scar lump after each treatment.

Clinical indications for stopping keloid drug injection therapy: (1) the clinical symptoms of pain and itching disappeared; (2) keloid color changed: from light red, dark red to close to normal skin; (3) the texture of the scar pimple changed: from the original hardness to softness; (4) the keloid atrophied, and the surface changed from the original hardness and smoothness to skin wrinkles.

2.2 | Surgical treatment of keloid scars

Some of the keloids were surgically reshaped after being treated with medication. Timing of surgery: Surgery was performed when the scar was in a stable state. The criteria for judging that the scar lump was in a stable state after drug treatment: (1) Color changed: the scar lump changed from the original dark red to a lighter color, that is, from the original state of blood filling and abundance to a state where the blood was not obviously filled. (2) Texture changed: the scar has changed from the original tough state to a softer state. The surface changed from the original bright state to a wrinkled surface. (3) Changes in volume: Keloids shrinked to varying degrees, and some keloids even completely subsided.

Most surgical methods were performed using keloid removal and scar tissue flap repair. After the operation, the tissue healed well, the skin at the original scar area was flat, and the skin color slowly recovered, close to normal skin tone.

2.3 | Laser treatment of keloids

After drug treatment, the scar lump did not completely subside, the surface was uneven, and after the keloid subsided, the surface was rough and not smooth, and the carbon dioxide laser grinding treatment was carried out. Laser treatment mode was performed in continuous or dot matrix mode. The timing of laser treatment for keloids was also chosen when the keloids were in a stable state after treatment.

After laser treatment at most lesions, the skin returned to near normal skin. A small number of uneven lesions appeared hyperplastic after laser treatment. This phenomenon mainly occured in continuous laser excision of protruding scars, and lasers caused excessive skin lesions. This phenomenon did not occur in dot matrix laser mode.

Keloid treatment flowchart: Step I Drug therapy, to make active hypertrophic scars and keloids into stable scars. After medication, some of the scars subsided and flattened, no further treatment was required. Scars with morphological deformities are further treated. Step II Laser or surgical treatment. Morphological repair of scars were done in the stable phase. Scars with uneven surfaces were treated with lasers. Keloids and scars that protruded from the skin were treated surgically.

TABLE 1 Correlation between the resolution of pain and itching of keloid and the size of keloid and the number of treatment. Small scars, pain, and itching symptoms subside quickly. Large scars resolve slowly. Small scars have symptoms subsided after 1–2 treatments, while large scars require multiple treatments to relieve symptoms.

TPI KA	First treatment	Second treatment	Third treatment	Fourth treatment and more
≤4cm^2	8 (9.2%)	11 (12.8%)	0	0
4–16cm^2	0	12 (13.9%)	14 (16.3%)	2 (2.3%)
>16cm^2	0	0	21 (24.4%)	18 (20.9%)

Abbreviations: KA: keloid area; TPI, time for pain and itching to subside.

Distribution of cases receiving different treatments at each stage:

	Drug therapy	Laser therapy	Surgical operation
Step I	86		
Step II		21	27

3 | RESULTS

3.1 | Changes in clinical symptoms

The pain of scars and itching symptoms have basically subsided through treatment, and the rate of regression was different. Mainly related to the size of the scar lumps, the lesions were smaller, the clinical symptoms subsided quickly, and they subsided after 1–2 injections. The lesion was larger and the clinical symptoms subsided slowly. This difference was mainly related to the limited dose of each drug use, the large area of the scar lump, and the fact that a single injection did not completely cover the diseased tissue.The time when the pain and itching of the scar lumps subside and the difference in various size scars were listed in Table 1.

3.2 | Keloid atrophy changes

The degree of atrophy was observed when a stable state was achieved after treatment.

After drug injection treatment, the degree of keloid atrophy was correlated with the height of keloid hyperplasia and bulge. Keloids with small bulges receded quickly, and keloids with high lift heights receded more slowly. Hyperplastic, highly raised scars did not resolve completely, but will atrophied to varying degrees.

Scars with a thickness of ≤4 mm can basically be flattened. The thickness of 5- to 7-mm scars and pimples subsided to varying degrees, some faded more, some faded less; Scars > 7 mm thick were difficult to resolve, and even if they did, the surface was uneven.The degree of keloid regression with different scar thicknesswas listed in Table 2.

TABLE 2 The degree of keloid regression with different scar thickness was shown. Keloids with small bulges receded quickly, and keloids with high lift heights receded more slowly. Scars less than 4-mm thick are flattened after treatment, scars with a thickness greater than 7 mm are difficult to flatten after treatment.

RR KT	100% regression	75% regression	50% regression	<50% regression
≤3mm	17 (19.8%)	0	0	0
3–5mm	11 (12.8%)	9 (10.5%)	10 (11.6%)	7 (7.9%)
>5mm	0	5 (5.8%)	11 (19.8%)	16 (18.6%)

Abbreviations: KT, Keloid thickness; RR, regression results.

TABLE 3 The keloid recurrence with different size of scar area and thickness was presented. Small keloids were treated with adequate courses of treatment and basically did not recur. Large, thicker keloids that have been treated for a longer period of time still recur. However, it is only a local recurrence. For scars with a scar area greater than 16 cm^2, the recurrence rate is only 6.9%–7.9%.

KT KA	≤3mm	3–5mm	>5mm
0–4cm^2	0	0	0
4–16cm^2	0	0	1(1.2%)
16–49cm^2	0	4 (4.7%)	6 (6.9%)
>49cm^2	0	3 (3.5%)	7 (7.9%)

Abbreviations: KA: keloid area; KT, Keloid thickness; RR, regression results; TPI, time for pain and itching to subside.

3.3 | Recurrence of scars

The follow-up period after keloid drug treatment was 2 years. Recurrence was judged by resurgence. The recurrence rate of keloids was related to the area of the keloids and the thickness of the hyperplasia. Keloids with small areas were treated with adequate courses of treatment and basically did not recur.

Large, thicker keloids that have been treated for a longer period of time still recur, and recurrence was manifested by hyperplasia of local keloids rather than hyperplastic hypertrophy of overall keloids. The recurrent site was again given drug injection therapy and continued to be treated until it was stable. The recurrence was observed for 1 year, and there was still a local recurrence in cases with an area of >49 cm^2. When counting cases, all cases that have had relapse are classified as relapsed cases. The keloid recurrence with different size of scar area and thickness is listed in Table 3.

The preoperation and postoperation of the lesion appearance are shown in Figures 1–3.

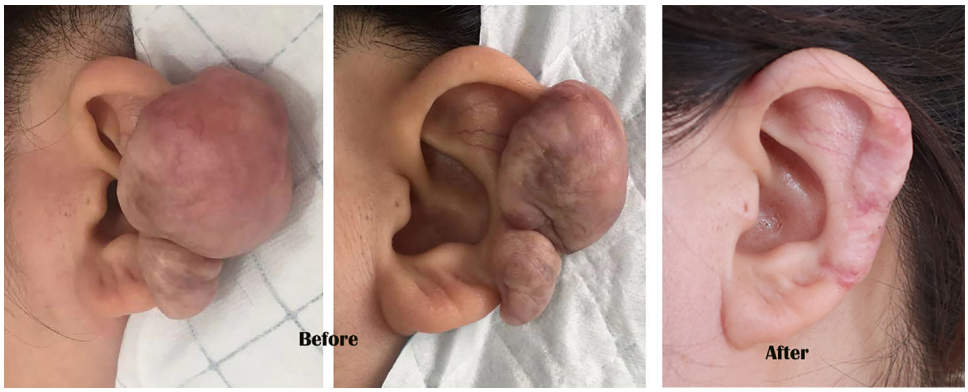

FIGURE 1 The appearance of the left ear keloid before treatment was shown. After treatment with bleomycin and triamcinolone acetonide, the erythema of keloid regressed, the keloid changed from hard to soft, and the surface of the keloid became wrinkled. The ear reconstruction was performed, the shape of the outer ear has basically returned to normal. Over the next 2 years of follow-up, the scar remained stable and did not recur.

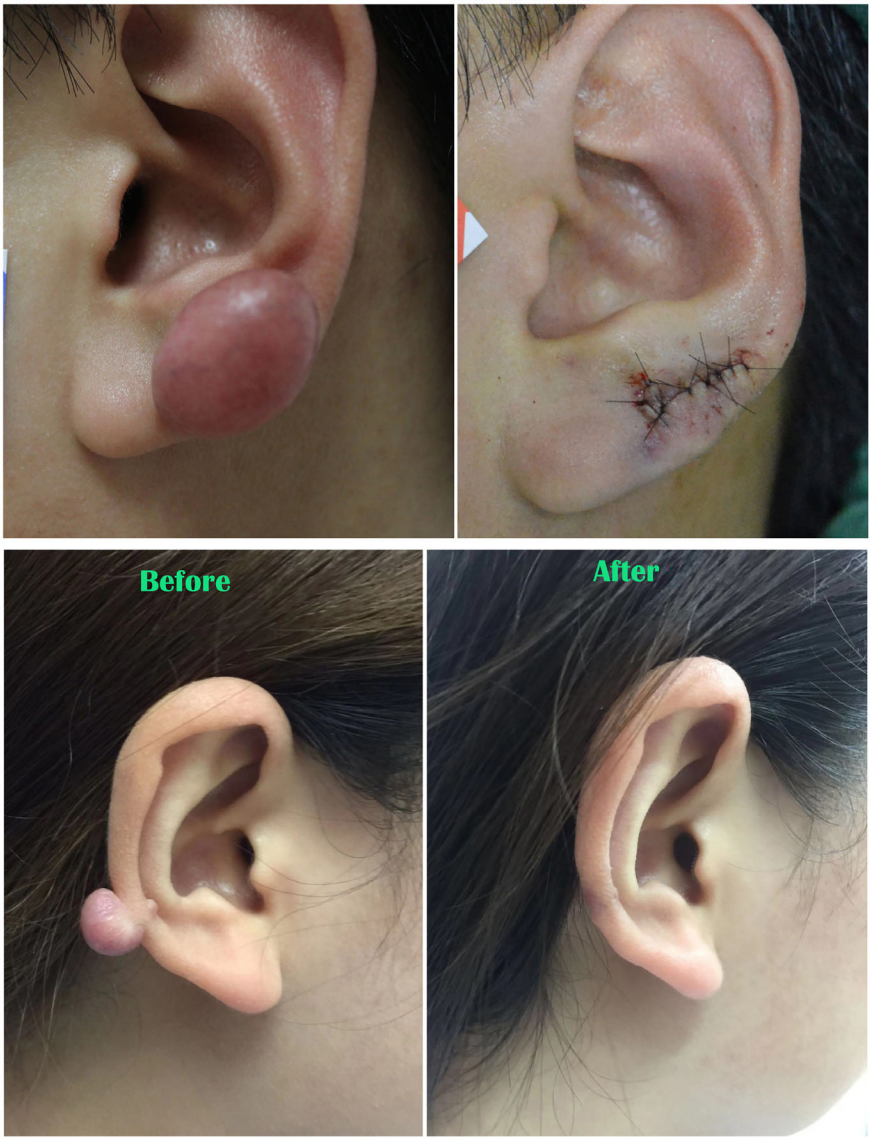

FIGURE 2 The ear scar keloid looks cherry red before treatment. Then the keloid was removed, and the auricle was repaired with scar flaps after bleomycin and triamcinolone acetonide treatment. The ears returned to normal. In the following 2 years, the shape of the outer ear did not change, and the scar did not recur.

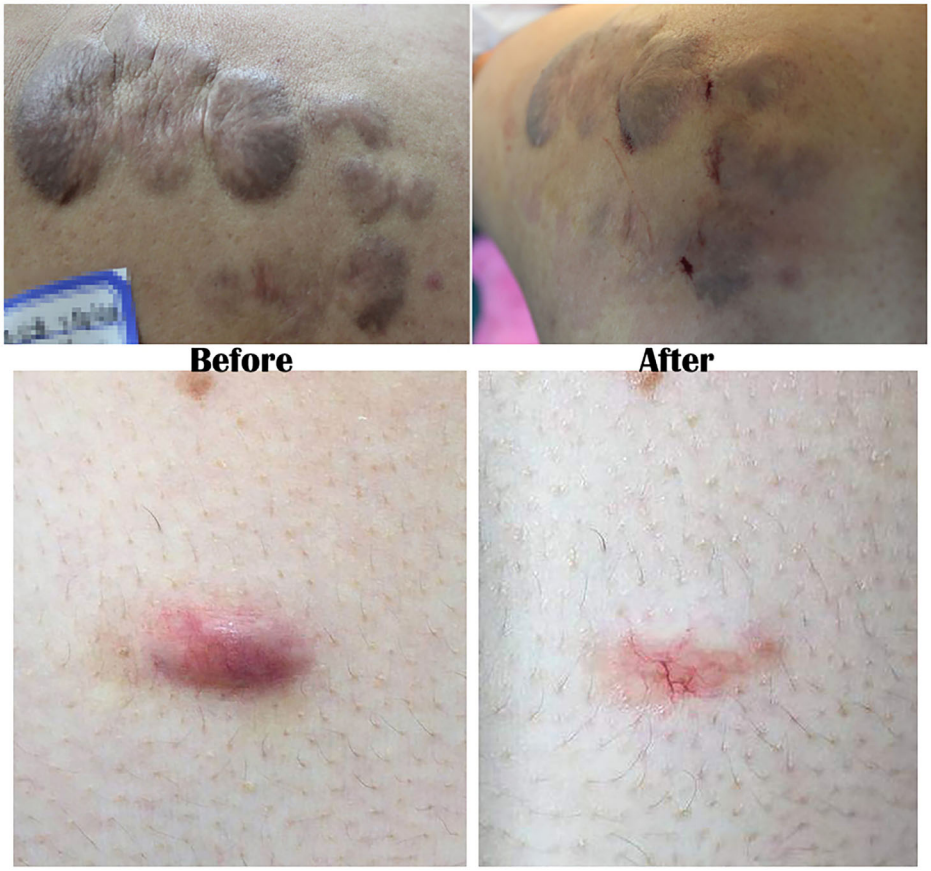

FIGURE 3 The keloid of right scapular and chest before treatment were visibly raised and plump. After bleomycin and triamcinolone acetonide treatment, the scapular keloid became flat and soft, the chest keloid disappeared. Over the next 2 years of follow-up, the scar remained stable and did not recur.

4 | DISCUSSION

Keloids and hyperplastic scar are difficult to treat, the most important thing is its recurrence, sometimes the recurrence of keloids is even larger than the original keloids, scars will invade the surrounding normal tissues. Current conventional treatments are difficult to work.

The treatment of keloids and hyperplastic scar include surgical treatment, hormone injection therapy, radiation therapy, laser treatment, cryotherapy, etc. Standard keloid treatment is surgery after hormone injections or followed by local radiation therapy. According to relevant clinical reports, the recurrence rate of scars and pimples is still high with this treatment method.[1]

We take the first drug injection treatment clinically (using bleomycin and triamcin acetonide) and carry out the necessary surgical treatment and laser treatment when the scar lumps after drug treatment are in a stable state and have achieved relatively good clinical results. This is mainly related to the use of bleomycin.

The mechanism of action of bleomycin is to bind to the DNA of the cell, causing the DNA strands to break, thereby blocking the division and proliferation of the cell; phase M cells are most sensitive to bleomycin.[2,3] In vitro experiments have shown that bleomycin can significantly disrupt cell division of fibroblasts.[4] These mechanisms of action of bleomycin are consistent with our clinical results.

Triamcinolone acetonide can effectively reduce the volume of scars when used in the treatment of scars. However, it is easy to recur when used alone for keloid treatment. In our clinical treatment, it is combined with bleomycin to achieve the effect of reducing the volume of keloids while effectively inhibiting their recurrence.

Bleomycin has been reported for the treatment of keloids[5–7] but not much.[8] Previous literature has not reported the combined use of bleomycin and triamcin acetonide in the treatment of keloids and hyperplastic scar. Our clinical exploration may provide an effective route for the treatment of keloids and hyperplastic scar.

The combination of bleomycin and triacinolone acetonide may relieve the pain and itching symptoms of keloids. Sometimes after only 1-2 treatments, symptoms were relieved. It also can inhibit the excessive proliferation of keloids and hypertrophic scars, promote scar atrophy and flattening, and prevent the recurrence of keloids and hypertrophic scars. After treatment, small and medium-sized scars no longer recur, large-area keloids are only local recurrences even if they recur.

In our clinical treatment, there is one thing to note: the course of drug treatment should be sufficient; otherwise it is easy to recur.

Although our clinical treatment has achieved good results, there are still aspects that need to be continued to be improved. In the treatment of keloids, we noticed a phenomenon: in areas 3 mm away from the injection site, the keloids would remain in their original state or continue to grow.

This reminds us that the drug has a short and difficult to spread within the scar. Scars with small areas are basically no recurrence after treatment; keloids with larger areas and thicker hyperplasia have some recurrences, which are manifested as local recurrences rather than all recurrences. This may be caused by uneven distribution of the drug during the medication process. From the perspective of the flat distribution, the distance between the injection needle puncture is too wide, the amount of drug in the middle site is insufficient, or the drug is missing; from the perspective of the thickness of the scar lumps, after hyperplasia, the keloids, when injecting drugs, only along a horizontal surface into the needle, the base of the keloids and the near surface of the scar, some areas are under-administered, or lack of drug coverage, resulting in insufficient treatment of some parts.

Of course, the recurrence of keloids may also be related to the biological characteristics of each keloid itself, and perhaps some keloid cells are more active, and their own microenvironment is more conducive to keloid recurrence. Next, we intend to improve the method of administration so that the drug can be better evenly distributed within the scar tissue.

5 | CONCLUSION

The combined application of bleomycin and triamcin acetonide can effectively eliminate the clinical symptoms of itching and pain of scars, make the scars atrophy and flatten, not recur. After treatment, small and medium-sized scars no longer recur; large-area keloids are only local recurrences even if they recur.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

FUNDING INFORMATION

The authors received no specific funding for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study plan and consent to participate were reviewed and approved by the ethics committee of Peking University, School and Hospital of Stomatology (in 2012, it was implemented as a filing system, but there was no serial number). All patients signed an informed consent form prior to treatment and agreed to use clinical data for academic communication and publication.

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