The Efficacy of Local Application of Mitomycin C in Reducing Recurrence Rate of Keloid after Surgery

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ABSTRACT

Introduction

Keloid is a hyperproliferative response of the fibroelastic connective tissue to dermal trauma, appearing predominantly in areas of high skin tension. Surgical excision produces immediate cosmetic correction, but recurrence rates after surgical treatment alone are high and post excision adjunct therapies should be considered. Topical application of Mitomycin C has shown to suppress cell division, fibroblast proliferation, protein and collagen synthesis and angiogenesis. In our study we applied it locally after surgical excision of keloid of auricle and compared the outcome with post-surgical perilesional Triamcinolone acetonide injection to reduce recurrence.

Materials and Methods

Fifty cases with primary or recurrent keloid over auricle were studied from February 2015 to January 2016. They are divided into two groups; Group 1 received local Mitomycin C application after keloid excision while Group 2 had perilesional injection of Triamcinolone acetonide after surgical excision of keloid. The results were compared 6 months after the initial treatment.

Results

There was no statistical difference in the baseline characteristics like age, sex, type of symptoms and previous history of recurrence between the two groups. Most of the patients in both the groups were aged between 14 and 30 years. The study population constituted predominantly of females. At the end of 6 months follow up, the recurrences noted were 5 and 6 respectively in Group 1 and 2 out of 25 patients in each group.

Conclusion

After surgical excision of keloid, topical application of Mitomycin C is as effective as intralesional Triamcinolone acetonide injection in terms of recurrence of the keloids affecting the auricle.

Keywords

Keloid; Ear Auricle; Mitomycin; Triamcinolone Acetonide; Recurrence

Keloid is a hyperproliferative response of the fibroelastic connective tissue to dermal trauma, appearing predominantly in areas of high skin tension. Keloids are the result of an abnormal wound healing process that lacks control over tissue repair and regeneration. They are cosmetically unpleasant and discomforting due to associated itching, tightness and tenderness and can cause significant morbidity. Keloids in the head, neck and face are highly conspicuous. Moreover, owing to their location, they cannot be easily covered. However, the most challenging aspect of management of keloids is dealing with their recurrence.

Surgical excision produces immediate cosmetic correction, but recurrence rates of surgical treatment alone are high and post-excision adjunct therapies should be considered. This includes post-operative topical application of 5-FU, Bleomycin, Mitomycin C. Post-operative treatment with immunomodulators like Imiquimod and interferon alpha-2b are also being studied. Preliminary reports of some of these adjunct therapies

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suggest potential benefit in preventing recurrence after surgery.

Mitomycin C has been isolated from Streptomyces caespitosus.[1] It is an alkylating agent which inhibits DNA synthesis in rapidly dividing neoplastic cells. It is used as an antineoplastic chemotherapeutic agent in treatment of upper gastrointestinal, breast and urinary bladder malignancies. Topical application of Mitomycin C has been reported in ophthalmic and endoscopic sinus surgeries to reduce scar formation.

In our study, we compared the effectiveness of immediate post-excision topical application of Mitomycin C with immediate post-excision Triamcinolone acetonide local injection therapy, and analyzed its potential in management of keloid of pinna.

Materials and Methods

Patients with primary or recurrent keloid over auricle, registered at the Department of Otorhinolaryngology and Head and Neck Surgery were studied from February 2015 to January 2016. A total 50 lesions in 40 patients, of which 10 have bilateral keloids, were included in the study. The patients were randomly divided into two groups and the treatment procedure and study protocol was explained to them. Twenty five cases were included in Group 1 and 25 in Group 2. Patients with primary or recurrent keloid over the auricular region, who consented to their inclusion, were included in this study irrespective of their age. Patients with known/ developed hypersensitivity to Mitomycin C or Triamcinolone acetonide were not included in the study. Patients with extensive keloids that cannot be excised by surgical excision under local anaesthesia and needed surgical intervention under general anaesthesia were also excluded from this study.

Group 1:

After proper positioning and local infiltration of the surgical site with 2% lignocaine with adrenaline (1:100000). After elevation of the skin flap, a part of it was left behind, and the core of the keloid was removed by sharp dissection. Cotton pledgets soaked in Mitomycin C in dilution of 1mg/ml were applied to the surgical wound for 5 minutes. Wound was then irrigated with normal saline. Tensionless wound closure was done using 5-0 monofilament polypropylene suture.

Group 2:

In group 2 patients, after surgical excision by similar method Triamcinolone acetonide (1 ml of 40mg/ml) was injected at the site of excision and surrounding area and post-operative dressing done.

Evaluation:

All the patients of both the groups were evaluated after 6 months and documented with photograph of the site (Fig. 1). A blinded surgeon not related to the study evaluated the result.

Results

The results obtained 6 months after the treatment were then compared between the two groups and chi square test applied where appropriate. P value smaller than 0.05 was considered significant.

The mean age of the sample was 28.5 years ranging from 14 to 52 years. The mean age of Group 1 was 27.2 years while that of group 2 was 29.8 years. Both the groups were statistically age matched by paired t test. Majority of the patients were female with only 2 male patients. All the patients had history of dermal trauma at the keloid site.

Majority of them had cosmetic complaints; others had itching, burning and pain at the site. Ten out of the 25 patients in Group 1 and 12 out of 25 in Group 2 had previous history of treatment and recurrence.

No significant association was found between history of recurrence on presentation and recurrence after the current treatment in either group.

Recurrence rates after treatment at the end of 6 months follow up were not significantly different in patients of postoperative Triamcinolone therapy compared to patients of post-operative Mitomycin C application by chi square test (Table I).

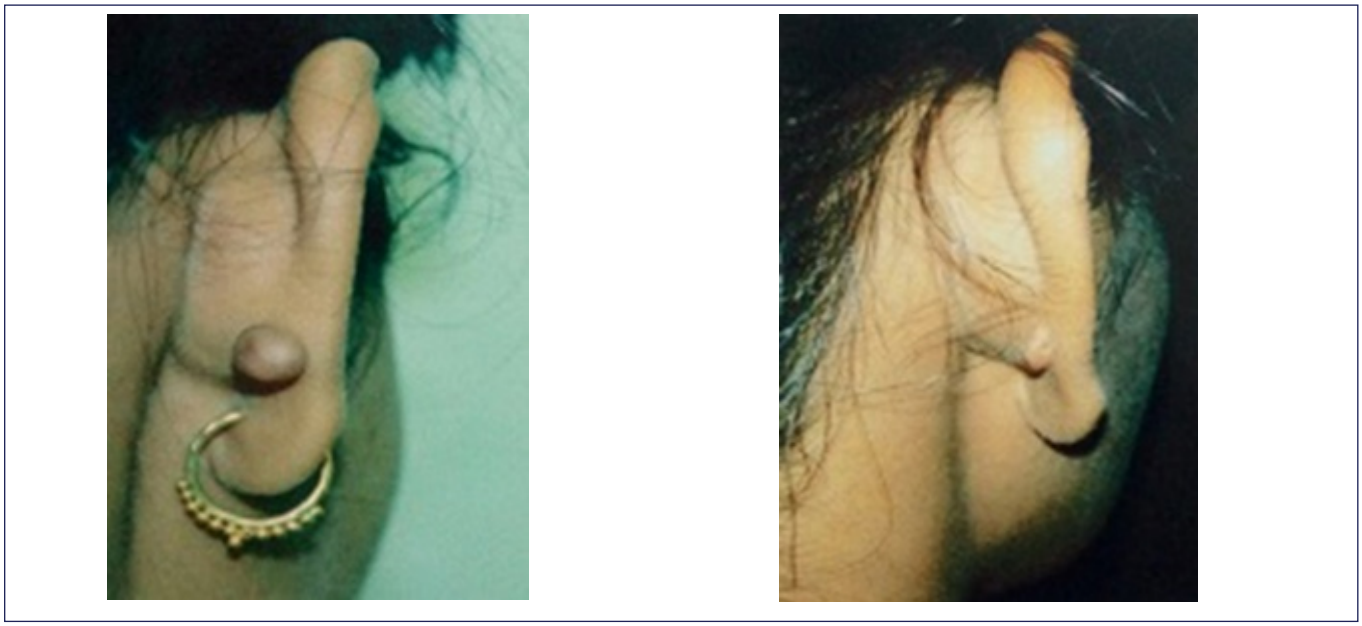

Fig.1. Preoperative and postoperative photographs (taken after 6 months follow-up) in a 25 year old female with right auricular keloid

Discussion

Keloid is a cosmetic blemish. A significant number of treatment modalities have been tried for successful cure of Keloids over the years. Therapeutic treatment of keloids includes occlusive dressings, compression therapy, intralesional corticosteroid injections, cryosurgery, Mitomycin C, excision, radiation therapy, laser therapy, interferon (IFN) therapy, 5-fluorouracil (5-FU), doxorubicin, bleomycin, verapamil, retinoic acid, imiquimod 5% cream, tamoxifen, tacrolimus, botulinum toxin, and over-the-counter treatments.[2] Surgical treatment gives immediate improvement in appearance and aesthetically pleasing results, but recurrence rate of surgery alone is relatively high, in the range of 45 to 100%.

Mitomycin C imparts antiproliferative effect on wound fibroblast through DNA synthesis inhibition. It can cause fibroblast arrest without sacrificing re-epithelialization. Mitomycin C when applied onto the mucosa immediately following dilatation of oesophageal and tracheal stenosis, would decrease re-stenosis by decreasing the production of fibroblast tissue and scar tissue.[3,4,5]

Egyptian surgeons around 1700 BC first described keloid.[6] Baron Jean-Louis Alibert (1768-1837) first reported it as an entity in 1806. He called them cancroïde, later changing the name to chéloïde to avoid confusion with cancer.[2] Incidence of keloids is more in the dark skinned people; the incidence being reported to be between 4% and 16% in the black population.[7] The ratio of type I collagen to type III collagen is elevated.[8] Keloids are fibrotic tumours containing relatively acellular centres and thick, abundant collagen bundles that form nodules in the deep dermal portion of the lesion.[9,10,11,12] Keloids are associated with significant pain, pruritus (itching), and physical disfigurement.[13] Recurrence after surgery poses a therapeutic challenge.

In concert with most other studies maximum number of patients with keloid in our study fall under the age group of 10 to 30 years.[14] Sex distribution in our study was in agreement with three other studies by Gupta et al[6] Chi et al[9] and Fruth et al[15] done on head neck keloid where majority of patients were female.

Finally, when the recurrence rates in the two groups were considered, we found that the recurrence rates in the Mitomycin C group were not significantly different as compared to the Triamcinolone group. Five

cases of recurrence were observed after post-surgical application of Mitomycin C, whereas 6 cases recurred after Triamcinolone injection. In one study Mitomycin C (0.4mg/ml) was topically applied after surgery for 4 minutes. 9 out of 10 patients had no recurrence after 8 months follow up.[16] Other study in which 20 patients were treated with surgical excision followed by

Table I : Comparison of the recurrence rates of keloid between the two groups

GROUP	RECURRENCE	NO RECURRENCE	TOTAL
Group 1	5	20	25
Group 2	6	19	25
TOTAL	**11**	**39**	**50**
p value = 0.7328 (Pearson's Chi square Test)			

Mitomycin C application for 5 minutes all 20 patients were satisfied after 14 months follow up and 2 showed complete disappearance of keloid. Contrary to this, in a study using patients as their own controls, Sanders et al reported that topical Mitomycin C application on excised keloid made no difference in recurrence.[1]

The mixed results of these trials may be related to small study sample size, different doses of Mitomycin C, different durations of follow up and lack of randomization. Sanders et al used Mitomycin C at a concentration of 0.4 to 0.5 mg/ml which made no difference in recurrence of keloid.[1] We used Mitomycin C in doses of 1mg/ml like many other studies and showed better results in terms of keloid recurrence. In concordance with many other studies no complications were observed with local application of Mitomycin C.[1,6,9,16]

Conclusion

Minimizing recurrence of keloids after surgery is of paramount importance. Combination of surgical excision with topical application of Mitomycin C is as effective as intralesional Triamcinolone acetonide injection in treating auricular keloids. Both of these two treatment modalities give far less recurrence rates compared with surgical treatment alone. So, these combination therapies are feasible options for management of keloid as they have very low recurrence rate and no significant adverse reaction.

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