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A novel approach of neoadjuvant and adjuvant therapy with surgery for large keloids of the ear

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ABSTRACT

Background: Ear keloids form after ear piercing in genetically predisposed young adults, causing cosmetic disfigurement and negative psycho-social impact, and reducing quality of life. Total excision of ear keloids leads to loss of ear tissue distorting ear framework and reconstruction to restore esthetically pleasant ear causes scarring and more aggressive keloids. Rate of recurrence is higher than 80% when surgical excision alone is done. **Aims and Objectives:** The study was conducted to compare the efficacy of intralesional triamcinolone acetonide (TAC) or 5-fluorouracil (5 FU) as monotherapy, combined TAC + 5 FU and multi-modal therapy (TAC + 5 FU + surgical excision) for keloids of the ear. **Materials and Methods:** The prospective comparative study included 30 patients who presented to the out-patient clinic of plastic surgery department of Government Mohan Kumaramangalam Medical College Hospital, Salem for a duration of 2 years from January 2021 to December 2022. Patients were categorized into three groups based on size of ear keloids, Group I (10) – Injection TAC (A) or 5- FU (B), Group II (10): Injection TAC + 5-FU, and Group III (10): Injection TAC + 5- FU + Surgical excision (A – neoadjuvant + adjuvant; B – only adjuvant). **Results:** Of a total of 30 patients, Group IIIA showed significant reduction of keloid with least side effects, most pleasing cosmetically (Patient and observer scar assessment scale 1/10). No recurrence in follow up. **Conclusion:** Multi-modal therapy consisting of neoadjuvant TAC + 5-FU, surgical excision, and adjuvant TAC + 5 FU offers the best long-term results for large ear keloids.

Key words: Ear keloids; 5 Fluorouracil; Triamcinolone; Ear piercing; Otoplasty

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INTRODUCTION

Keloids are pathological scars being an enigma for the surgeon, one of the most difficult to treat. Till date, there is no absolute single method that assures 100% success.[1] Recurrence following conventional treatment methods such as triamcinolone and surgical excision is alarmingly very high.[2] Ear keloids form after ear piercing in genetically predisposed young adults, causing cosmetic disfigurement and negative psycho-social impact, and reducing quality of life. Total excision of ear keloids leads to loss of ear tissue distorting ear framework and reconstruction to restore esthetically pleasant ear causes scarring and more aggressive keloids (re-bound effect). Rate of recurrence is higher than 80% when surgical excision alone is done for ear keloids.[2]

Aims and objectives

The purpose of this present study was to prospectively compare the efficacy of intralesional triamcinolone acetonide (TAC) or 5-fluorouracil (5 FU) as monotherapy, combined intralesional TAC+5 FU and multi-modal therapy (intralesional TAC+5 FU+surgical excision) for keloids of the ear.

MATERIALS AND METHODS

This was a prospective randomized control (double-blind) study conducted at the department of Plastic and Reconstructive Surgery, Government Mohan Kumaramangalam Medical College Hospital, Salem, Tamil Nadu, India, after the Institutional Ethics Committee

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approval. Study was conducted on 30 patients who presented to OPD of Department of Plastic surgery, GMKMCH, Salem, Tamil Nadu, India, with ear keloids. Study was done for a duration of 2 years from January 2021 to December 2022 after obtaining informed and written consent from participants.

Inclusion criteria

The following criteria were included in the study:

- All patients with ear keloids >12 years
- All sizes of ear keloids
- Single/multiple keloids in same ear
- Keloids in ear lobe, helix
- Keloids in single ear/both ears
- Previous history of other treatments or surgeries for ear keloids before 6 months with recurrence or residual keloids.

Exclusion criteria

The following criteria were excluded from the study:

- Patients <12 years (pediatric population)
- Co-morbidities: Diabetes Mellitus (Type I and II), hypertension, Coronary artery disease, liver disease, renal failure, autoimmune, and other systemic inflammatory diseases
- Pregnant and lactating patients
- Hypersensitivity or known drug reactions to TAC/5-FU
- Patients not willing for treatment and protracted follow-up
- Ulcerated and infected keloids.

All patients were subjected to complete history taking and examination included site, size, shape, color, and consistency of the lesion. Complete blood count, liver, and kidney functions were investigated before treatment and then at a monthly interval during therapy. The patients were informed about the nature of each procedure, expected number of treatments, and also expected side effects of the procedure. The patients were categorized into three groups based on the size of ear keloids (Table 1).

Equipments

1. BD Luer-Lok™ 1 mL syringe with a fixed 26 gauge needle to avoid potential needle disengagement, medication leakage, or spray during intralesional injection
2. Injection Lignocaine HCl 2% (LOX™, Neon pharma)
3. Injection 5-FU (5 FLUCEL™ 500, Celon labs) (Table 2)
4. Injection TAC (Kenacort™ vial, Abbott healthcare Pvt Ltd) (Table 2)

- Groups I and II: Six intralesional injections given every 21 days on out-Patient basis
- III-A: Surgery as a "sandwich" procedure. Three intralesional TAC+5 FU (1:9) injections given as a "Neo-adjuvant" every 21 days on OP basis. Surgical excision done and post-surgery intra-scar 3 injections given at 3 week intervals as an adjuvant therapy
- III-B: Surgery as an "antecedent" procedure. Ear keloid excised at initial presentation followed by post-operative intra-scar injection TAC+5-FU as an adjuvant therapy every 21 days for three sessions on OP basis

Intralesional injection technique

Initially, local anesthetic (lignocaine HCl 2%) was infiltrated at keloid site before intralesional/intra-scar injections. Then, multiple intralesional injections were given at 1 cm intervals, on an average 0.3 mL/cm^2 to ensure that the drug spreads throughout the entire lesion. TAC or 5-FU was injected from several directions directly into the keloid with care taken not to inject under the keloid mass or too close to epidermis to avoid unnecessary local side effects. The injection was infiltrated into the lesion until blanching occurred (Figure 4).

Surgical excision technique and post-operative protocol

Surgical excision was done under local infiltration anesthesia (lignocaine 2%+adrenaline 1: 100,000). In earlobe keloids, wedge resection with incision along margins of keloid anteriorly and posteriorly to earlobe and primary closure/local flap repair was done. In auricular cartilage (helix) keloids, core excision was done where entire fibrous core of keloid excised completely and sent for histopathological examination (Figure 5). After achieving complete hemostasis, wound closed primarily with simple interrupted or vertical mattress sutures using 5–0 ethilon and pressure dressing applied. Suture removal was done 15 days post-surgery after wound healed well. Patients were advised scar massage and 12 mm pressure ear-clips to be worn throughout the day for compression for minimum 1 year post-operation (Figure 6). Post-operative adjuvant intra-scar injections were started in Group III on 15th POD.

Assessment of the clinical response to treatment (seven parameters)

Assessment of keloids was done at every OP visit and during the subsequent follow-up period. Clinical changes in keloids were recorded by photographs and any side effects the patients experienced were reported.

1. Patient and observer scar assessment scale (POSAS) v 2.0: POSAS is a validated scar scale which measures the scar quality by evaluating visual (e.g., color), tactile (e.g., pliability), and sensory (e.g., itch) characteristics of the scar from the perspective of both the observer and

Table 1: Patients categorization into three groups based on size of ear keloids

Group	Category	Sub-groups	Number of patients	Modality/treatment	Keloid size
I	Intralesional injection MONOTHERAPY	IA	5	TAC alone [Figure 1]	SMALL (<2 cm) [Figure 2]
		IB	5	5-FU alone [Figure 1]	
II	COMBINED injection therapy (TAC+5 FU)		10	TAC+5 FU (1: 9) [Figure 1]	LARGE (2–4 cm) [Figure 2]
III	MULTI-MODAL therapy (TAC+5 FU+Surgical excision)	IIIA	5	Neo-adjuvant → Surgery → adjuvant TAC+5 FU	SEMI-MASSIVE and MASSIVE (>4 cm) [Figure 3]
		III B	5	Surgery → adjuvant TAC+5 FU	

Table 2: Pharmacological profile of intralesional drugs used in the study

Intralesional injection	Concentration	Maximum dose/session
5-fluorouracil (5-FU)	50 mg/mL	2 mL-100 mg
Triamcinolone acetonide (TAC)	40 mg/mL	2 mL-80 mg

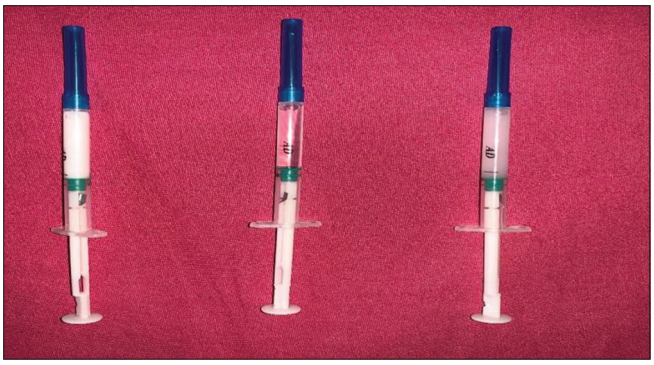

Figure 1: TAC alone, 5 FU alone, and TAC+5-FU (1:9) combination for intralesional injection

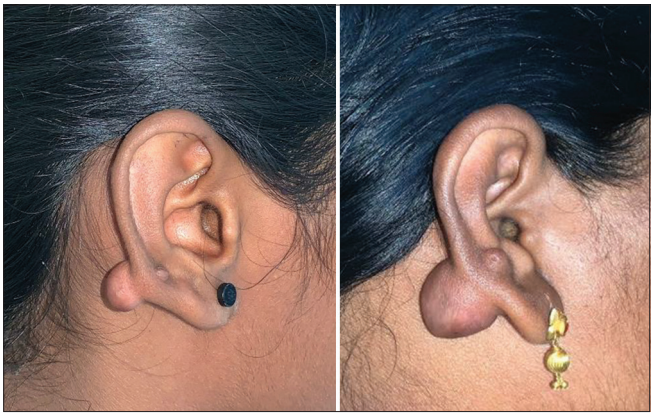

Figure 2: Group I-small (<2 cm) and Group II-large (2–4 cm)

patients. Sensory characteristics can only be accurately reported by the patient, so the observer scale only contains only the visual and tactile characteristics of scar. Patient scale contains items concerning the visual, tactile, and sensory characteristics of the scar. Each patient filled out patient component of POSAS scale at each visit every 3 weeks.

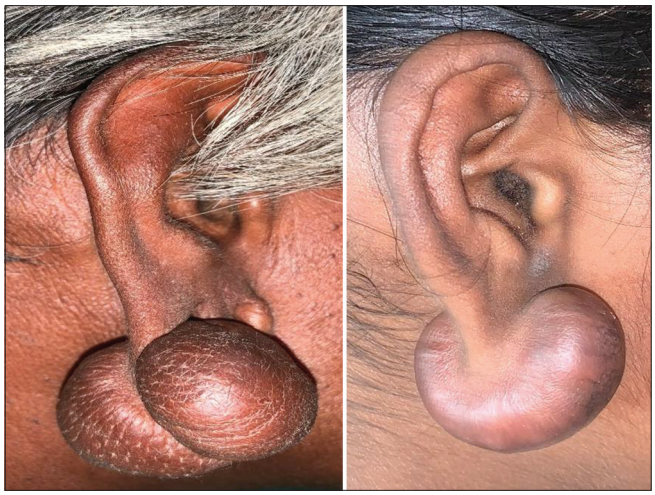

Figure 3: Group III-semi massive and massive (>4 cm)

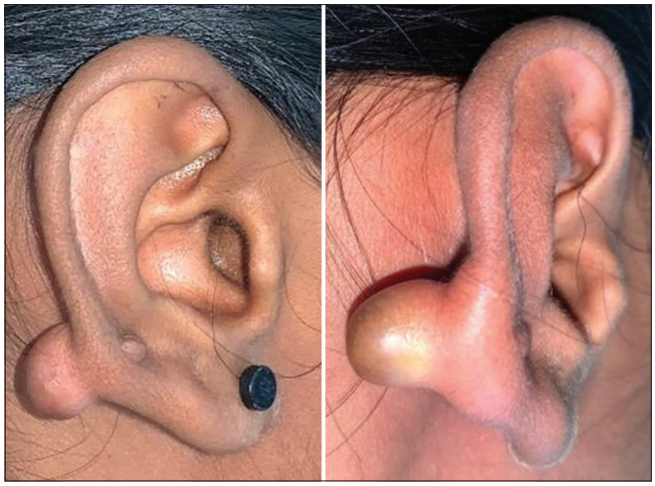

Figure 4: Intralesional injection was given till blanching occurred

POSAS observer scale consists of 6 parameters namely vascularity, pigmentation, thickness, pliability, relief, and surface area which are compared to normal skin on a comparable anatomic location(www. posas.org).[3]

2. Average reduction of keloidal mass size/tumor burden
3. Symptoms alleviation-reduction of pain and pruritus
4. Side effects
5. Intraoperative difficulties encountered and post-surgery complications (Group III)
6. Esthetic restoration of auricular architecture (observer

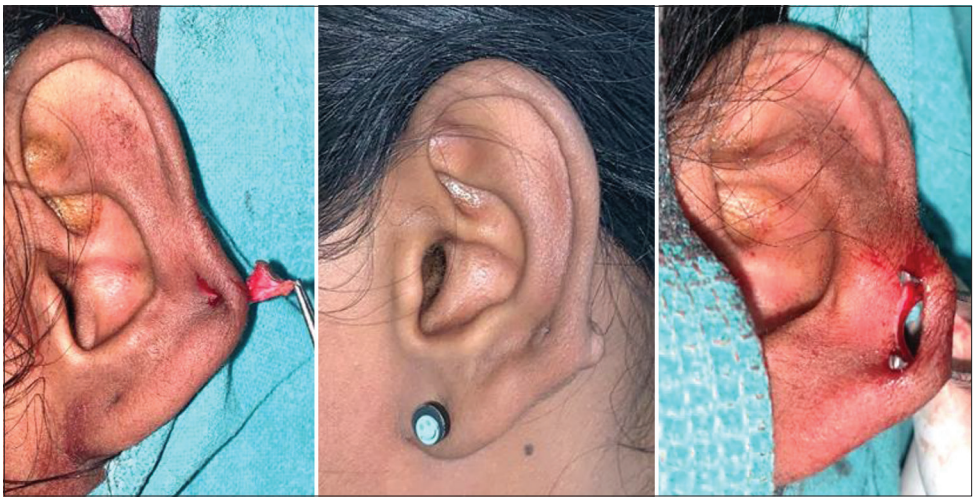

Figure 5: Core excision of auricular helix cartilage keloid: Coring out entire fibrous keloidal tissue from surrounding normal elastic cartilage and preserving normal helical rim

Figure 6: Post-operative scar management: 12 mm keloidal pressure application ear-rings[7]

and patient's cosmetic satisfaction) recorded as (1) poor, (2) fair, (3) good, (4) pleasant, and (5) excellent.

7. Recurrence the patients were followed up every month in out-patient for a period of 1 year after stopping treatment to look for residual keloidal lesion or recurrence in keloid scar site and other possible complications if any.

RESULTS

All 30 patients (100%) in our study were females might be probably due to high prevalence of the practice of cosmetic ear piercing in our region. Among females, it is a sociocultural factor. All ear keloids were a consequence of cosmetic ear piercing. Trauma and burns were not seen as etiological factors in patients participating in our study. Youngest female of all patients was 12 years of age who had bilateral recurrent earlobe keloids following previous surgical excision and the oldest was 80 years who had a huge single earlobe keloid.

Eighty percentages of females presented to us as initial consultations whereas the remaining 20% were either previously given intralesional TAC injections alone elsewhere as single random treatment without any follow-up and without any significant reduction in keloid size or surgical excision was done or keloid had relapsed.

Pain and itching were the most common presenting complaints besides increasing size. Pain was described as pricking type. Fourteen were painful and ten presented with pruritus. Six complained of both pain and itch. Cosmetic deformity was invariably perceived by all females as it was concerning their ears.

Ear keloids formed on an average 5 years after piercing was done. Longest time period between ear piercing and keloid formation was 20 years as seen in one case. Keloids were bilateral in ten patients whereas remaining had single ear keloids. In bilateral keloids, eight patients had keloids of different sizes in both ears. Only one patient presented with semi-massive ear keloid >6 cm. Unfortunately, this patient was an elderly female who lost to follow-up (Figure 7).

Standard earlobe was the commonest site of keloid (as it is also the most common site of cosmetic ear piercing). Out of 30, 20 patients had keloids of earlobe, 15 had keloids of helix (10-descending helix and 5-superior helix), 5-upper lobe. About 50% of patients who had ear lobe keloids also had keloids of helix. In 40% of patients, only helix was involved, sparing the earlobe even though piercing was done at both sites (Figure 8). Cartilage bearing portion of ear is more likely to form keloids due to its piercing in or after adolescence and prolonged wound healing caused

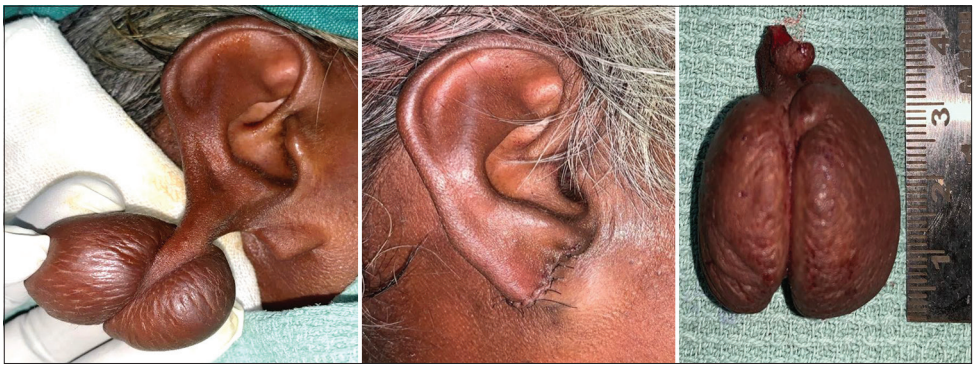

Figure 7: 80 years female; Semi-massive earlobe keloid 5×5 cm more than 50% of surface area of ear (Group III). Wedge resection with incision along margins of keloid anteriorly and posteriorly to earlobe and primary local flap repair done. Unfortunately the patient lost to follow-up

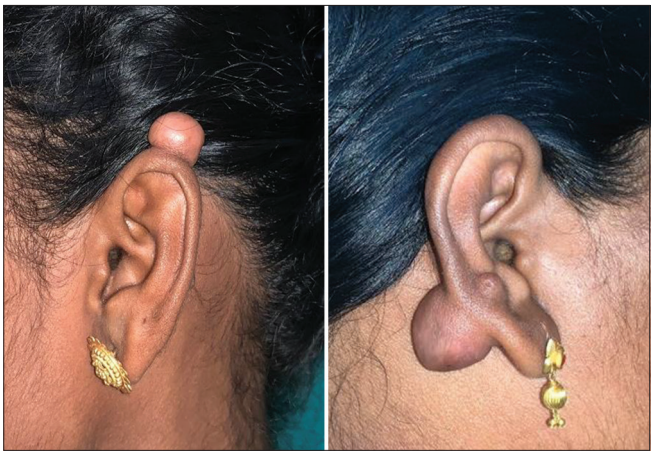

Figure 8: Only helix involved, sparing earlobe even though piercing was done at both sites

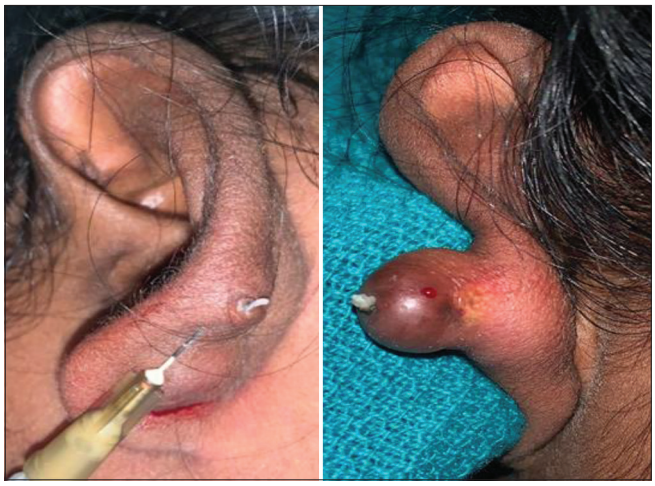

Figure 9: Inclusion cyst like material during intralesional injection from site of ear piercing (center of keloid)

by infection. In seven cases of helix keloids, sebaceous material was observed to emanate from the center of keloid (site of piercing) during intralesional injection. Probably, ear piercing caused invagination of epidermis and subsequent infection led to inclusion cyst formation within the keloid (Figure 9).

Reduction of keloidal mass size

TAC alone: Group (IA) did not lead to significant reduction in keloid size in four out of five patients with dimensions remaining more or less the same even after two injections of TAC monotherapy (Table 3).

5-FU alone: Group (IB) caused keloidal cell death and necrosis leading to significant softening (increased pliability), shrinkage, reduction of keloidal mass, and flattening of lesion. Color change was consistent causing dusky/blackish discoloration/dry gangrene with one or two injections. Keloidal tissue necrosis was more evident around the sites of needle prick for intralesional injection. Fortunately, the necrosis spared the normal earlobe/helix tissue (Table 3 and Figure 10).

TAC+5 FU – Group (II), on the other hand, caused tumor shrinkage comparable to 5-FU and also had the advantage of minimizing side effects due to TAC and 5 FU components per se (Table 3).

There was no correlation noted between age, duration of disease, and clinical outcome. Success of 5-FU in reducing keloid size in those cases that failed steroid treatment is particularly significant.

Side effects of injections

5-FU caused ulceration and transient hyperpigmentation in three out of five patients, but did not have any occurrence of hypopigmentation or telangiectasias. In five cases, there was superficial ulceration immediately following injection (might be probably due to 5 FU spreading too superficially beneath epidermis) causing blistering and peeling of skin. Such ulcers healed well with topical antibiotic ointments (Figure 11).

TAC component caused telangiectasias, skin atrophy, and hypopigmentation (Figure 12). Adverse effects in all patients

Table 3: Final observation statistics of ear keloids in various groups

Clinical parameter	Group IA	Group IB	Group II	Group IIIA	Group IIIB
Average reduction in lesion size*/flattening	30–50	45–75	70	95	85
Symptom alleviation					
Pain	60	74	90	100	95
Pruritus	55	70	94	95	92
POSAS scale	7/10	6/10	5/10	1/10	3/10
Recurrence	60	45	30–40	5–10	10–15
Ear cosmetics					
Observer evaluation	Poor	Poor	Fair	Excellent	Good
Patient perception	Poor	Poor	Good	Pleasant	Pleasant
Side effects of injections	+++	+++	++	-	+
Intraoperative difficulties (Group III)	-	-	-	+	+++

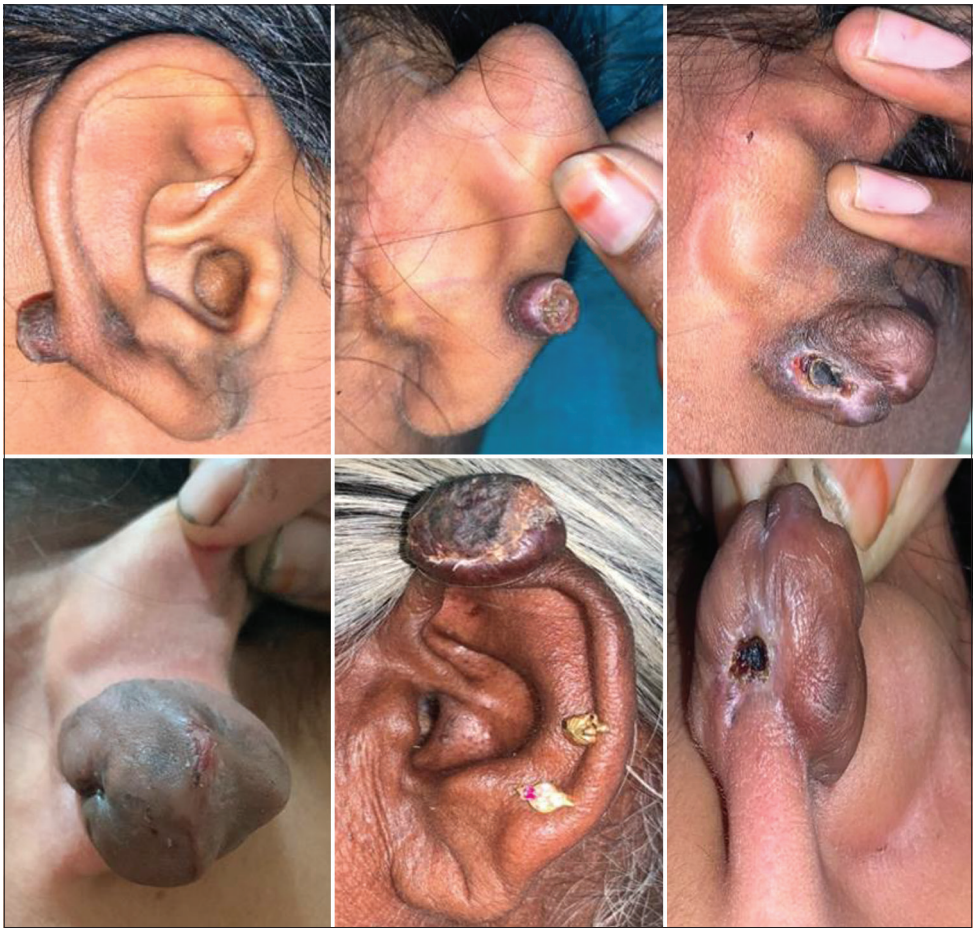

Figure 10: 5-FU caused local tissue necrosis and ulceration of keloid leading to significant flattening, shrinkage and skin discoloration. Gangrene of tumor mass was more in peri-injection area of the tumor

who received 5-FU were 23% as compared with 15% in steroid only group. Side effects of TAC or 5-FU alone as monotherapies were decreased without compromising efficacy using a 9:1 mixture of 5-FU and TAC in combined therapy as advocated by Fitzpatrick[11] (Table 3).

Four patients reported increased pain after injections after local anesthetic effect weaned off. Pain was more severe with 5-FU than TAC. No systemic reactions were found after local injection.

Esthetic restoration of normal auricular framework

Even though intralesional injections reduced keloid size, only in one patient with earlobe keloid, there was complete shrinkage of lesion with four sessions of TAC+5-FU with no recurrence in follow-up. This was the only case where there was no need for surgery to achieve significant keloid reduction or to restore normal auricular shape (Figure 12). In all other cases, normal auricular shape and complete keloidal mass elimination could be achieved only with surgery (Group III) (Table 3 and Figure 13).

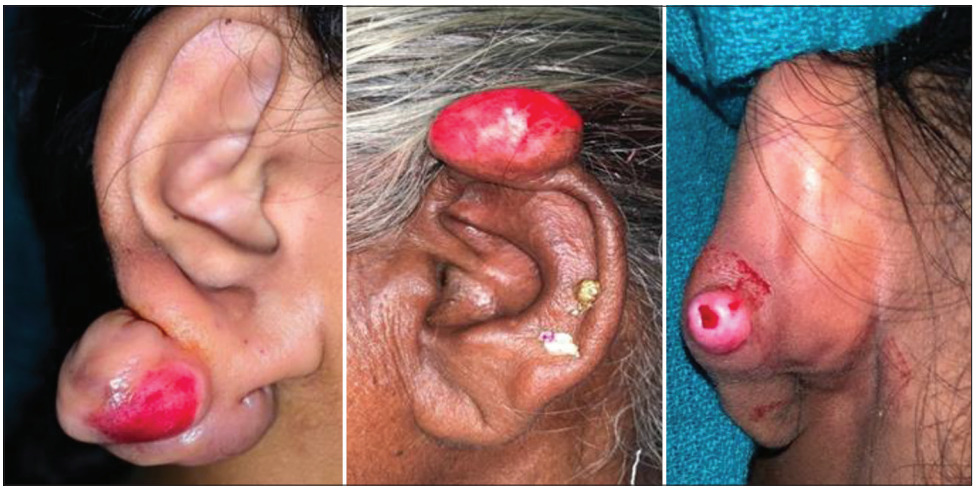

Figure 11: Superficial skin peeling and ulceration immediately after 5-FU injection

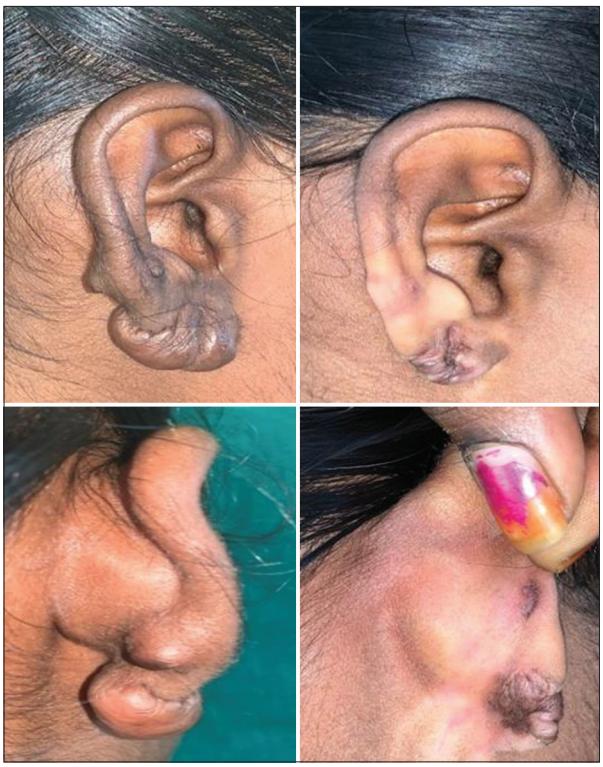

Figure 12: 1 case with significant keloidal mass reduction (>95%) with restoration of earlobe esthetics in combined intralesional TAC+5 FU(Group II). Hypopigmentation and skin atrophy was due to TAC component. Darkening was due to 5-FU

Intraoperative difficulties and post-surgery complications (Group III)

During surgical excision, the loss of substance of the earlobe had to be reconstructed by re-approximation of edges leading to cosmetic difference compared to the contralateral side. When the patient was taken up for antecedent surgery (Group IIIB) when the keloid is "immature angry red looking and huge," excessive intraoperative bleeding was noted. This hindered precise and complete lesion excision.There was more loss of earlobe

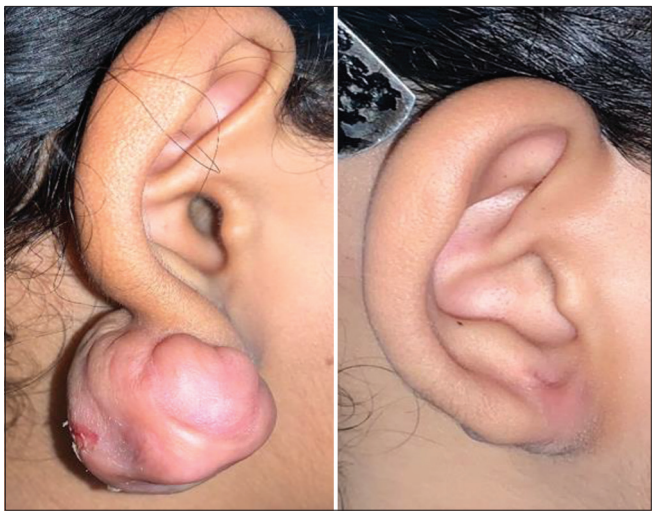

Figure 13: Group III B: A case of recurrent semi-massive earlobe keloid following surgery. Long term follow up at 1 year showing no recurrence, a stable mature scar with good preservation of earlobe esthetics

substance after excision, troubling esthetic reconstruction. Whereas in Group IIIA, where surgery was done after three sessions of intralesional neoadjuvant injections with 5-FU and TAC (9:1), keloid became more supple, soft, and "more mature" with reduced vascularity (as evident by reduced blanching). There was less intraoperative bleeding and less loss of ear substance and surgery was technically more comfortable and less demanding. This is similar to the effect of "Neoadjuvant" chemotherapy in which the tumor is down-staged and size is reduced (shrinkage of tumor) before definitive surgical excision. In one case, there was post-operative wound dehiscence when sutures were removed on POD-15 (Table 3).

Cost of drugs and ease of administration

5 mL of 50 mg/mL 5-FU is cheaper than 1 mL of triamcinolone 40 mg/mL. Hence, 9:1 combination of 5 FU and TAC seems logical and cost-effective compared

with other expensive modalities such as cryotherapy and radiotherapy. Intralesional injections can be administered by the surgeon himself with minimal discomfort to the patient under local anesthesia as an outpatient procedure in the office setup itself without requirement of additional workforce or skilled technician.

Repeat ear piercing was allowed to be done in patients after ensuring no recurrence in 1 year follow-up.

DISCUSSION

Keloids are due to excessive scarring presenting pathologically as nodular firm lesions that extend beyond area of injury causing severe itching and pain.[5] Unlike hypertrophic scars, they fail to spontaneously regress, often continuing to grow permanently and worsen over time. Keloids reach enormous sizes when left apart without adapted treatment. The probability of recurrence of keloids after surgical removal alone is very high, usually >80%.[2] The prevalence of earlobe keloid is higher in the Asian skin than in the Caucasian skin. The global risk of keloid formation is highest in the black-skin/African population.[6]

Abnormal wound healing process results from lack of control mechanisms self-regulating cell proliferation and tissue repair. Keloids lead to cosmetic embarrassment and functional impairment causing psychological trauma and affect quality of life. Most frequently affected body areas are chest, shoulders, ear, and upper back.[1]

Conventionally, intralesional TAC injections have been shown to induce keloid regression.[6] Side effects with TAC are common and significant with telangiectasias, hypopigmentation, and skin atrophy reported in 37%.[7] Combining corticosteroid injections with 5-FU, pulsed-dye laser, or cryotherapy have better outcomes than corticosteroid injections alone.[6] Many studies have been done till date comparing TAC and 5-FU in general for keloid treatment.[7] There is a broad range of reported dosing intervals, from several injections per week to once a month.[6]

Silicone dressings are least invasive, but strong and reliable evidence for its efficacy is lacking. Cryotherapy (monotherapy or with TAC injection) effectively reduces keloid size.[5] Methods include direct contact, sprays, and intralesional needles. However, supporting evidence is limited to case series.[5]

Resemblance of keloids to malignant growth patterns and their hyper-metabolic state was used in searching for other minimally invasive, low-risk treatments; 5-FU is an anti-neoplastic (anti-mitotic) agent which blocks synthesis of the pyrimidine thymidine, which is a nucleoside necessary for DNA replication. Scarcity of thymidine monophosphatase results in thymidine-less death in rapidly dividing cells, thus inhibiting collagen synthesis and reducing aberrant scarring.[7]

A special region is the ear. Ear keloids can form after cosmetic ear piercing, trauma, or burns, and have distinctive esthetic and sociocultural implications. Earlobe keloids usually appear as shiny, smooth, and globular growths on one or both sides of the earlobe.[8] Ear piercing is by far the leading triggering factor for ear keloid formation in genetically predisposed individuals. Review of literature shows only one study done by Chinese which investigated whether intralesional injection of low-dose 5-FU and corticosteroid can increase effective rate and decrease recurrence rate of surgically removed auricular keloid.[1]

Tirgan classification of ear keloids[9]

- Massive: Size of keloid mass is greater than the surface area of the corresponding ear
- Semi-massive: The size of the keloid mass is at least 50% of the surface area of the corresponding ear, but smaller than massive ear keloids
- Large: The size of the keloid mass was more than the size of the corresponding earlobe, but smaller than semi-massive ear keloids
- Small: The size of the keloid mass is less than the size of the corresponding earlobe.

Total surgical excision of ear keloid leads to noticeable loss of ear/earlobe tissue. While surgical reconstruction is the only possible way to restore an esthetically pleasant ear in these patients, it is associated with more tissue damage, scarring, and development of more aggressive keloids at all operative sites.[2]

Lyu et al., investigated surgical methods for the removal of larger ear keloids. Two different surgical techniques were used: Method A, tumor excision followed by *in situ* scar flap repair; and Method B, wedge resection of an auricular lesion followed by primary closure or local flap repair. After the treatment, patients received post-operative, local radiotherapy. He concluded keloid scars can be effectively treated with a combination of radiotherapy and method B of surgical excision-more ears cured with least recurrence.[10]

Wedge excision is recommended for earlobe keloids.[8] A case series study of earlobe keloids showed that wedge excision and radiotherapy yielded 4.7% recurrence at 18 months. Core excision is recommended for auricular cartilage keloid. A case series showed that core excision of auricular keloid plus steroid injection yielded 9.5% recurrence rates at 22 months.[10]

Ideal ear keloid treatment should have a low side effect profile, be cost effective, easy to administer, and minimally invasive, which should eradicate the lesion as much as possible without causing significant esthetic distortion of ear and most importantly have least recurrence.[2]

Pain after 5 FU injection can be reduced by combining EMLA, MEOPA, and hypnose.[7]

In Group IA only 40% remission of lesion, patients were not esthetically satisfied and there was residual lesion with more side effects reported.

In Group- IB, 60% remission noted. This is in accordance with the previous studies.[7]

In Group II, 70% reduction of symptoms noted. Cosmetic improvement was better and side effects lesser than Group I. recurrence rate was lesser than Group I (40%). 5-FU in combination with triamcinolone (Group II) may be superior to triamcinolone alone (Group IA). This is in conformity with other studies.[5]

Group III-A: (Surgery as a sandwich procedure)-significant reduction of keloidal mass size and symptoms. Least side effects of injections compared to all other groups. Intra operative complications were lesser compared to group IIIB. Patients were most satisfied with cosmetically pleasant results.

Group III-B: (Surgery as an antecedent procedure): Intraoperative bleeding with difficulty in excision and loss of ear tissue with cumbersome reconstruction and post-injection side effects were more compared to IIIA.

Comparison made in our study within Group III is a novel type of categorization and analysis not made in any other studies reported in the literature. Study done by Wu et al.,[1] concluded that surgical removal of auricular keloid followed by intralesional injection of low-dose 5-Fu and steroid is an effective method to treat auricular keloid and prevent its relapse. However, it was not a comparative study and surgery was not done as a sandwich in his study.[1]

Limitations of the study

Sample size in our study has been limited to 30. There might have been a selection bias as patients were subjected to different modalities of treatment based on sizes of ear keloids.

CONCLUSION

For small ear keloids, intralesional TAC+5 FU injections can cause significant reduction of size and symptoms and in some cases complete lesion eradication without significant side effects. In large, semi-massive and massive ear keloids, TAC+5 FU can achieve reduction of keloidal mass size, but complete elimination of tumor and restoration of auricular esthetics is possible only with multi-modal therapy. Neoadjuvant TAC+5 FU before surgical excision followed by adjuvant TAC+5 FU offers the best long-term results for large ear keloids in terms of complete lesion eradication, reduction of symptoms, least recurrence, esthetic pleasantness, easier administration with least side effects, less intraoperative difficulties, cosmetic reconstruction, minimal post-surgical complications, and cost-effectiveness.

Sample size in our study has been limited. Further studies with larger sample size are required to establish efficacies of multi-modal therapies for ear keloids with such novel categorizations. Given the ethnic differences in pathologic scar propensity, prevention and treatment algorithms should be optimized for each human race by means of international collaboration.

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