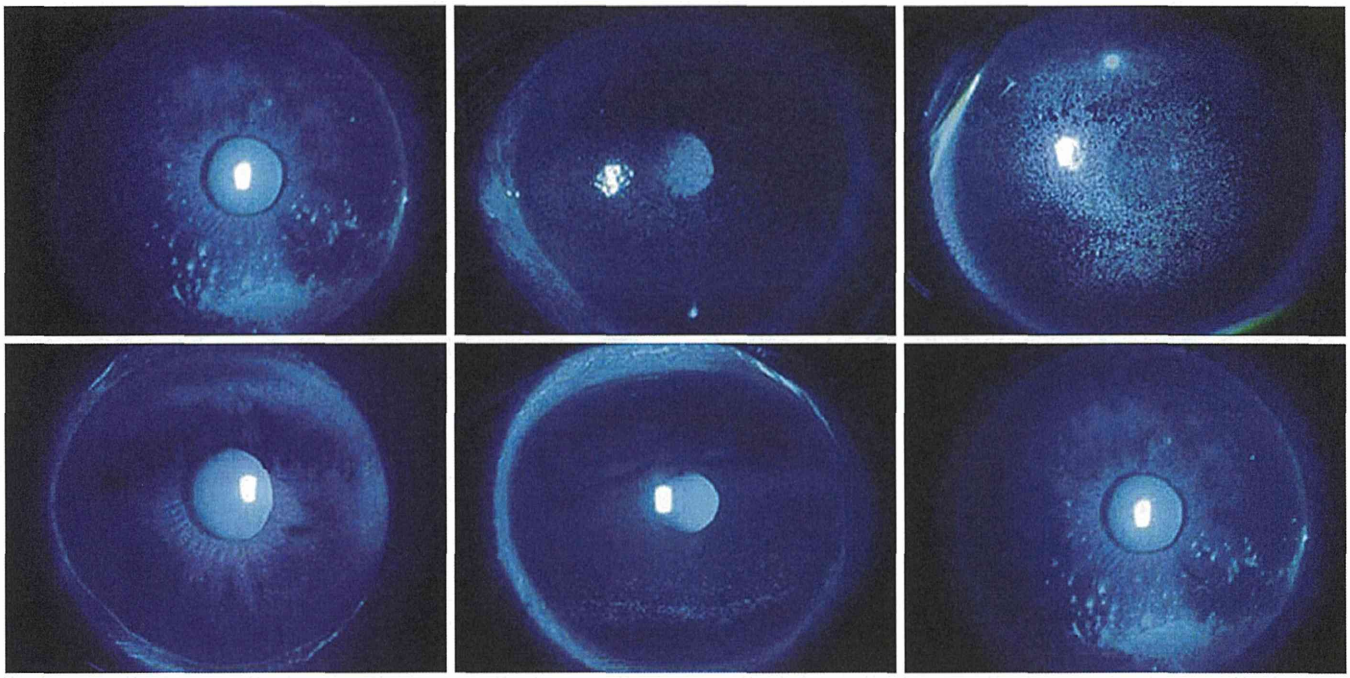

FIGURE 1. Images showing the area (A) and density (D) classification of the fluorescein staining score for evaluating superior limbic keratitis in patients with thyroid eye disease. The Top column shows grading for the area and the Bottom column shows grading for the density: (Top left) A1D3, (Top middle) A2D3, (Top right) A3D3, (Bottom left) A1D1, (Bottom middle) A1D2, and (Bottom right) A1D3. The area of superficial punctate keratopathy was graded as A0 when there was no punctate staining, A1 when the staining involved less than one third of the cornea, A2 when it involved one third to two thirds of the cornea, and A3 when the staining involved more than two thirds of the cornea. The density of superficial punctate keratopathy was graded as D0 when there was no punctate staining, D1 when the density was sparse, D2 when the density was moderate, and D3 when the density was high and the lesions overlapped.

least 2 of the following criteria were diagnosed with SLK: blood vessel dilation in the superior bulbar conjunctiva, papillary inflammation of the upper tarsal conjunctiva, punctate rose bengal and fluorescein staining of the superior conjunctiva and of the upper cornea, filaments in the upper cornea, epithelial thickening of the superior bulbar conjunctiva, and redundancy of the superior bulbar conjunctiva.[7,9] Patients wearing contact lenses or with other treatment for TED, dry eye, or both between pretreatment and posttreatment evaluations[7] were excluded from this study. All patients had received topical rebamipide (Mucosta ophthalmic suspension unit dose 2%; Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan; chemical name, (2RS)-2-(4-chlorobenzoylamino)-3-(2-oxo-1, 2-dihydroquinolin-4-yl) propanoic acid), 1 drop in each eye 4 times daily.

The information collected from the patients' medical records included patient age, sex, and thyroid function evaluated before treatment. The severity of ocular surface conditions as well as TED conditions before and 4 weeks after the start of treatment were examined because response peak of rebamipide generally is at 4 weeks.[1] The presence or absence of SLK, rose bengal staining score,[31] area and density classification of fluorescein staining,[32] Schirmer test I results, and tear film break-up time (TBUT) were assessed. Rose bengal staining was evaluated in the temporal and nasal conjunctiva and the cornea, then quantified on a scale of 0 (no staining) to 3 (severe staining).[31] Thus, the maximum score that could be obtained from the staining of 1 eye was 9. The evaluation method of fluorescein staining is shown on Figure 1. The Schirmer test was performed without anesthesia as follows. A Schirmer test strip was placed on the lower conjunctival sac without touching the cornea for 5 minutes, and the length of the wet portion was measured. To determine TBUT, a drop of 2% fluorescein solution was instilled in the lower conjunctival sac. The time from normal blinking to the first appearance of a dry spot in the tear film was measured.

Hertel exophthalmometry values, margin reflex distance (MRD) 1 and MRD-2, and a 7-point scale of the clinical activity score (CAS)[33] for assessment of TED condition also were determined. In Hertel exophthalmometry measurements, distance from the corneal apex to a plane defined by the deepest point on the lateral orbital rim was measured. A base value, the distance between the 2 footplates, was documented at the first measurement and reproduced at the follow-up examinations. MRD-1 and MRD-2 were measured as the distance from the upper

TABLE 1. Data from Thyroid Eye Disease Patients with Superior Limbic Keratoconjunctivitis, Measurements of Ocular Surface Conditions, and Statistical Comparisons

No. of eyes/patients	33/20
Right/left	15/18
Male/female	4/16
Age (range), y	43.4 ± 11.0 (26 to 66)
No. of patients	
With hyperthyroidism	6
With euthyroidism	14
Hertel exophthalmometry (range), mm	16.7 ± 2.2 (12.5 to 21.0)
MRD-1 (range), mm	4.9 ± 1.5 (3.0 to 10.5)
MRD-2 (range), mm	5.7 ± 0.9 (3.5 to 8.0)

	Before Treatment	After Treatment	*P* Value
Presence of SLK (no. of eyes)	33	5	**< .001**[a]
Rose bengal staining score (range)	2.8 ± 1.0 (2 to 6)	0.8 ± 1.1 (0 to 4)	**< .001**[b]
AD classification			
A (range)	1.4 ± 0.7 (0 to 3)	0.3 ± 0.5 (0 to 1)	**< .001**[b]
D (range)	1.5 ± 0.8 (0 to 3)	0.4 ± 0.7 (0 to 2)	**< .001**[b]
Schirmer test results (range), mm	13.2 ± 8.6 (0 to 31)	14.5 ± 10.4 (0 to 35)	.212[c]
TBUT (range), s	2.8 ± 1.4 (1 to 7)	3.5 ± 2.0 (2 to 8)	**.009**[c]

AD = area and density; MRD = margin reflex distance; SLK = superior limbic keratoconjunctivitis; TBUT = tear film break-up time.
Boldface values indicate statistical significance.
[a]Fisher exact probability test.
[b]Wilcoxon signed-rank test.
[c]Paired *t* test.

(MRD-1) or lower (MRD-2) eyelid margin to the corneal light reflex in the primary eye position. The patient was set in the sitting position with brow fixation and was requested to look at a light source (a pen torch),[34] then the distances were recorded using a millimeter ruler. The CAS consists of 7 parameters, including retrobulbar discomfort, pain on eye movement, eyelid erythema, eyelid swelling, conjunctival injection, chemosis, and swollen caruncle.[33] When the CAS was 4 points or more, it was defined as active TED.[33] All examinations were performed by one of the authors (H.K.).

Patient ages and measurement values were expressed as the mean value ± standard deviation. The presence of SLK was compared before and after treatment using the Fisher exact probability test. The Wilcoxon signed-rank test was used to compare the rose bengal staining scores and the area and density classification scores before and after treatment. The paired *t* test was used to compare the results of the Schirmer test and TBUT before versus after treatment. We compared Hertel exophthalmometry values after treatment and MRD-1 and MRD-2 between eyes with or without SLK at the 4 week follow-up examination using the Mann–Whitney *U* test. The presence of proptosis of more than 17.7 mm (the upper limit of the Japanese normal proptosis value)[35] and upper (the upper eyelid margin located above the upper corneal limbus) and lower (the lower eyelid margin located below the lower corneal limbus) eyelid retraction were compared between eyes with or without SLK at the 4-week follow-up examination using the Fisher exact probability test. Statistical analysis was performed using SPSS II software for Windows (SPSS Japan, Inc, Tokyo, Japan). $P < .05$ was considered statistically significant.

RESULTS

THIRTY-THREE EYES FROM 20 PATIENTS (15 RIGHT EYES AND 18 left eyes; 4 men and 16 women; mean age, 43.4 ± 11.0 years; range, 26 to 66 years) were included in this study (Table 1). All patients had taken antithyroid drugs before starting rebamipide treatment. Six of 20 patients (30.0%) continued to exhibit signs of hyperthyroidism, whereas the other 14 (70.0%) were considered to be controlled euthyroid patients. Before treatment, 10 (6 patients) of 33 eyes (30.3%) exhibited Hertel exophthalmometry values of more than 17.7 mm. Ten (7 patients) of 33 eyelids (30.3%) and 12 (9 patients) of 33 eyelids (36.4%) showed upper and lower eyelid retraction, respectively. All patients were judged as having inactive TED on the basis of the CAS. These results had not changed at the 4-week follow-up.

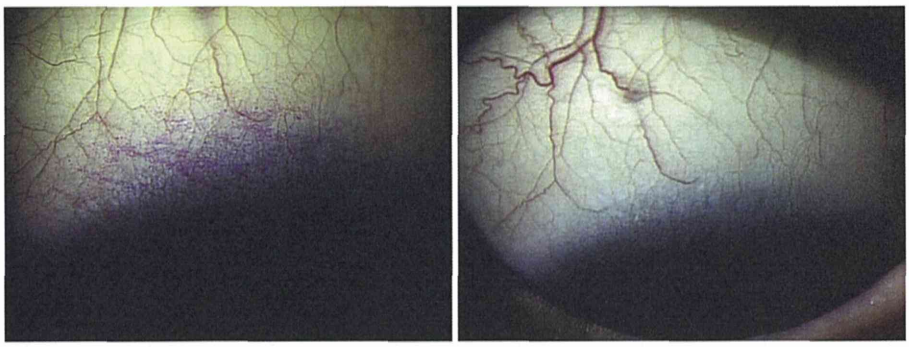

FIGURE 2. Slit-lamp photographs of the left eye of a 38-year-old woman with thyroid eye disease. (Left) Pretreatment photograph showing punctate rose bengal staining and injection of the superior conjunctiva. (Right) Posttreatment photograph revealing no punctate rose bengal staining and conjunctival injection.

TABLE 2. Comparison of Proptosis and Upper and Lower Eyelid Positions between Eyes with or without Superior Limbic Keratoconjunctivitis at the 4-Week Follow-up

	After Treatment		
	SLK Positive	SLK Negative	*P* Value
Total no. of eyes	5	28	
Proptosis > 17.7 mm, no. of eyes (%)	2 (40.0)	8 (28.6)	.485[a]
Hertel exophthalmometry (range), mm	17.6 ± 2.3 (15.0 to 21.0)	16.6 ± 2.2 (12.5 to 21.0)	.407[b]
Upper eyelid retraction, no. of eyes (%)	4 (80.0%)	6 (21.4%)	**.021**[a]
MRD-1 (range), mm	6.1 ± 0.4 (5.5 to 6.5)	4.7 ± 1.5 (3.0 to 10.5)	**.007**[b]
Lower eyelid retraction, no. of eyes (%)	1 (20.0%)	11 (39.3%)	.388[a]
MRD-2 (range), mm	5.8 ± 1.3 (5.0 to 8.0)	5.7 ± 0.8 (3.5 to 8.0)	.530[b]

MRD = margin reflex distance; SLK = superior limbic keratoconjunctivitis.
Boldface values indicate statistical significance.
[a]Fisher exact probability test.
[b]Mann–Whitney *U* test.

Although SLK was present before treatment in all patients, treatment completely resolved signs in 28 eyes (84.8%; $P < .001$; Figure 2 and Table 1). In the other 5 eyes (15.2%), punctate rose bengal staining near the upper corneal limbus remained, but decreased substantially. Each of these 5 eyes exhibited at least 1 of the following findings: proptosis of more than 17.7 mm and upper and lower eyelid retraction. Upper eyelid retraction was more prevalent in eyes with SLK than in those without SLK at the 4-week follow-up ($P = .021$; Table 2). After treatment, MRD-1 was significantly larger in eyes with SLK than in those without SLK at the 4-week follow-up ($P = .007$). The difference in Hertel exophthalmometry values after treatment, MRD-2, and the number of eyes with proptosis of more than 17.7 mm or lower eyelid retraction was not significant between eyes with and without SLK at the 4-week follow-up ($P > .050$).

For the group overall, rose bengal staining was reduced significantly after treatment ($P < .001$; Table 2). Both area scores ($P < .001$) and density scores ($P < .001$) also decreased significantly after treatment. The Schirmer test results were similar before and after treatment ($P = .212$). TBUT increased significantly after treatment ($P = .009$).

Two patients (10.0%) reported a bitter taste after the instillation of topical rebamipide, but nonetheless continued treatment. No serious adverse events were reported.

DISCUSSION

REBAMIPIDE TREATMENT INDUCED SIGNIFICANT IMPROVEment of SLK signs in all eyes and complete remission in 84.8% of eyes after treatment. These results indicate that rebamipide was effective for the treatment of SLK in TED patients.

Rebamipide increases production of mucin-like substances in the cornea and conjunctiva, suppresses expression of cytokines, and attenuates tumor necrosis factor-α-induced barrier disruption in the corneal epithelium.[1–6] Because local mucin deficiency in the upper conjunctiva and inflammation between the upper eyelid and the superior corneal limbus

are main etiologic factors in SLK,[7,8] these functions of rebamipide may be efficacious for SLK.

Eye drops for corneal protection and topical α-blockers, as well as oral nonsteroidal anti-inflammatory drugs, were effective only in two thirds of SLK patients with TED,[10] but the remaining one third of the patients required systemic steroids, radiation therapy, blepharoplasty, strabismus surgery, and orbital decompression for improvement of SLK.[10] Because all patients in this study were in an inactive phase without an indication of systemic steroids and radiation therapy, the results cannot be compared simply with those of previous studies.[10] However, rebamipide is suggested as an alternative, first-line treatment for SLK in TED patients because of its much higher improvement rate.

SLK signs persisted in 5 eyes (15.2%) that showed a higher incidence of upper eyelid retraction and larger MRD-1 values than eyes without SLK after the treatment. Upper eyelid retraction caused excessive tear evaporation as well as a taut upper eyelid, which may lead to the refractory cases of SLK observed in the present study.[10,13,14] Rebamipide does not affect the watery portion of lacrimal fluid; thus, no improvement in the Schirmer test results was noted in this study.[1] Additional topical treatments, such as artificial tears and diquafosol,[3] may represent better options in intractable cases to supply the watery portion lost by evaporation. Additional topical immunosuppressive agents (cyclosporine A and tacrolimus) may suppress inflammation more strongly between the upper eyelid and the superior corneal limbus. Orbital decompression and eyelid lengthening surgeries may be viable alternatives,[9,10] but the surgical indication of these procedures may be limited in SLK patients with disfiguring eyelid malposition and proptosis, lagophthalmos, and compressive optic neuropathy.[36]

Hertel exophthalmometry values, MRD-2, and the number of eyes with proptosis of more than 17.7 mm or lower eyelid retraction were not significantly different between eyes with and without SLK at the 4-week follow-up. Proptosis and lower eyelid retraction may not be influential factors in treatment of SLK in TED patients.

Because no serious side effect was shown during topical rebamipide treatment in the present and previous studies,[1,2] rebamipide should be considered a safe treatment for SLK.

In this study, we assessed severity of ocular surface conditions at 4 weeks after treatment. However, because SLK exhibits a chronic inflammatory component,[7,16] continuous treatment and long-term observations are required.

Our study was limited by several factors. This study was retrospective in nature and did not include a control group. The small sample size was another limitation. Although we evaluated TED conditions using the CAS, the CAS is a subjective scale of evaluation.[33] We did not perform impression cytologic analysis, which would have provided more helpful information on assessment of efficacy of rebamipide treatment.[15]

In conclusion, rebamipide was an effective treatment for SLK in TED patients and may be chosen as a first-line treatment in these patients.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. Involved in Design of study (Y.T., H.K.); Conduct of study (Y.T., H.K.); Analysis and interpretation of data (Y.T., A.I., H.K.); and Preparation and review of manuscript (Y.T., A.I., H.K.).

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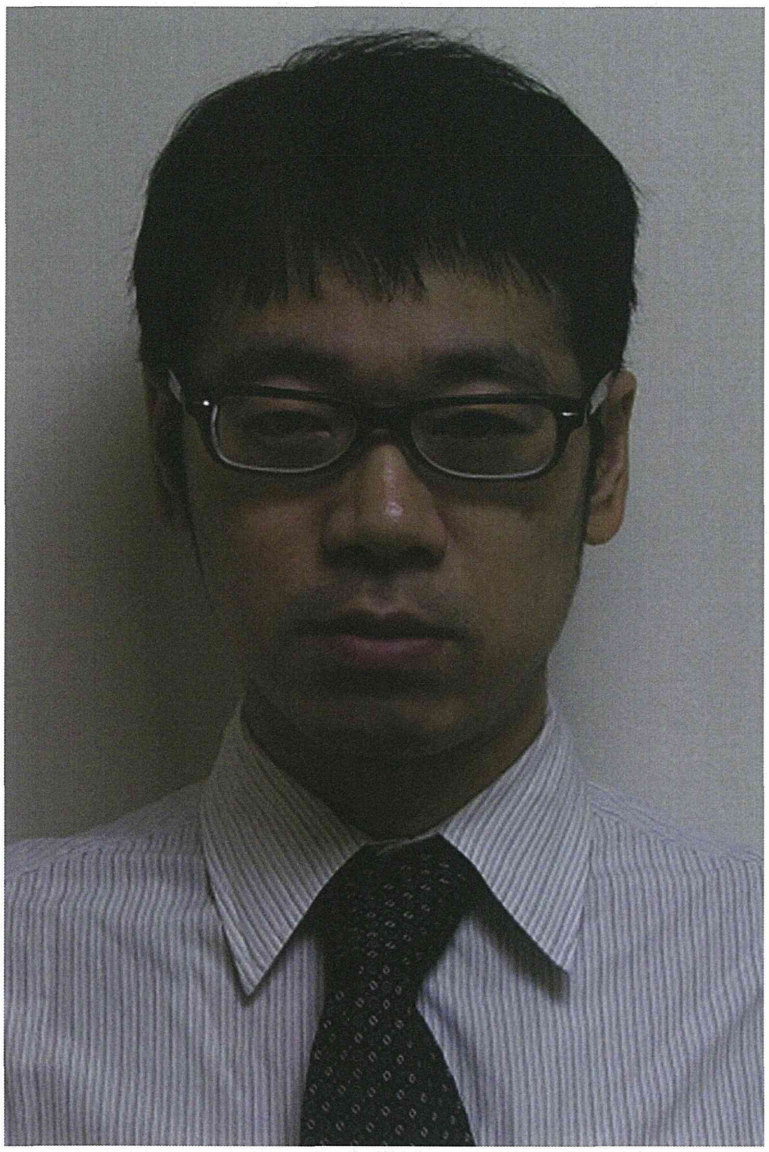

Biosketch

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Biosketch

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Combination of Nasolabial V-Y Advancement Flap and Glabellar Subcutaneous Pedicled Flap for Reconstruction of Medial Canthal Defect

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Key Words

Basal cell carcinoma · Nasolabial V-Y advancement flap · Glabellar subcutaneous pedicled flap · Medial canthal defect

Abstract

A 77-year-old woman presented with a 1-year history of a right medial canthal tumor, which was histopathologically diagnosed as a basal cell carcinoma. After removal of the tumor with a 4-mm safety margin, the defect occupied the areas superior and inferior to the medial canthal tendon. We first reconstructed the lower part of the defect using a nasolabial V-Y advancement flap to make an elliptic defect in the upper part. We then created a glabellar subcutaneous pedicled flap to match the residual upper elliptic defect with the major axis set along a relaxed skin tension line. The pedicled glabellar flap was passed through a subcutaneous tunnel to the upper residual defect. At 6 months postoperatively, the patient showed no tumor recurrence and a good cosmetic outcome.

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Introduction

Reconstruction of medial canthal defects is challenging. The donor site is limited around the medial canthus, which results in excess skin traction and distortion [1]. Although a basic principle of an eyelid reconstruction is the use of neighboring tissues for matched skin color and texture, medial canthal reconstruction involves two different facial esthetic units: the areas superior and inferior to the medial canthal tendon (MCT) [2]. A single-unit flap occasionally yields a cosmetically unsatisfactory appearance.

We herein report a case of a medial canthal defect including the areas superior and inferior to the MCT, which were separately reconstructed using a nasolabial V-Y advancement flap and a glabellar subcutaneous pedicled flap.

Case Presentation

A 77-year-old woman presented with a 1-year history of a black tumor in the right medial canthal region. The tumor measured 3 × 5 mm at the first examination. An incisional biopsy revealed that the tumor was a basal cell carcinoma.

We excised the tumor with a 4-mm safety margin (fig. 1a). The defect included the areas superior and inferior to the MCT and was adjacent to the medial eyelid commissure (fig. 1b). We planned to separately reconstruct the upper and lower parts of the defect using a nasolabial V-Y advancement flap and a glabellar subcutaneous pedicled flap (fig. 1c). We first advanced the nasolabial V-Y flap from the inferior aspect to create an elliptic defect in the upper part and fixed it to the dermis using 6-0 PDS® II sutures (Johnson & Johnson K.K., Tokyo, Japan) (fig. 1d). We then created a glabellar subcutaneous pedicled flap to match the residual upper elliptic defect with the major axis set along a relaxed skin tension line (fig. 1d). A subcutaneous tunnel was made between the flap and the defect, and the flap was passed through the tunnel to the upper residual defect (fig. 1e). The resultant defect in the glabella was closed in a dermostitch fashion with 6-0 PDS® II (fig. 1f). Each flap was anchored to the MCT to create a concavity in the medial canthal region. The skin was sutured with interrupted 6-0 polyvinylidene fluoride sutures (Asflex®; Kono Seisakusho Co., Ltd., Tokyo, Japan) (fig. 1g).

The excised tissue margin was histopathologically free of tumor cells. At 6 months postoperatively, no tumor recurrence or deformity was evident, and only an inconspicuous scar was present (fig. 1h).

Discussion

The medial canthal defect presented here was separately reconstructed using a combination technique of a nasolabial V-Y advancement flap and a glabellar subcutaneous pedicled flap. This technique was performed according to both the basic principles of eyelid reconstruction and the esthetic unit of the face.

We first advanced the nasolabial V-Y flap to create an elliptic defect in the upper part, and then created the glabellar flap to match the defect. These procedures created a concavity in the medial canthal region and spared skin trimming. The small flap size produced little traction at the donor sites. The major axis of the glabellar flap and a part of the V-Y flap corresponded to the relaxed skin tension line and the nasolabial fold, respectively, resulting in inconspicuous scars.

A glabellar transpositional flap is a standard technique for medial canthal reconstruction [3]. However, there are several drawbacks, such as deformity due to a thick flap, vertical conspicuous scarring in the glabellar region, change in the brow position, and the necessity of skin trimming. Other single-unit flaps from the upper eyelid, radix nasi, or nasolabial region occasionally cause web formation across the medial canthal concavity [4, 5]. A large single flap may yield excess traction and distortion of the donor site in contrast to combination flap techniques.

In conclusion, a combination of a nasolabial V-Y advancement flap and a glabellar subcutaneous pedicled flap resulted in successful reconstruction of a medial canthal defect including the areas superior and inferior to the MCT with a good cosmetic outcome. Eyelid reconstruction may be accomplished with good outcomes when performed according to basic reconstruction concepts and the facial esthetic unit.

Disclosure Statement

The authors have no financial interest related to this paper.

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