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REVIEW

# Ablative laser assisted topical delivery of antifibrotics in the management of cicatricial ectropion

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## Abstract

A variety of surgical techniques have traditionally been used to manage cicatricial ectropion. These techniques primarily aim at vertical lengthening of the anterior lamella and include a variety of skin flaps and grafts. Alternative techniques such as dermal filler injection to support the eyelid margin may also be used in the management of select patients with cicatricial ectropion. The application of different types of laser for scar revision throughout the body has rapidly evolved; similar mechanisms, principles and treatment rationale can be applied to the use of lasers in the management of cicatricial ectropion. Additionally, ablative lasers, such as Carbon Dioxide and Erbium:yttrium-aluminum-garnet lasers, may be used in the transdermal delivery of antifibrotic agents, such as interferon gamma, interferon alpha, vitamin D, triamcinolone and 5-fluorouracil, resulting in efficient target tissue penetration, limitation of systemic drug toxicity and decreased degradation. Although the combination of ablative fractional resurfacing and topical antifibrotic agents is a new treatment modality, there is a great potential for its efficient utility in the management of periocular scarring and cicatricial ectropion. The introduction of these innovative therapeutic modalities offers ophthalmologists a greater range of possible effective treatments to address periocular scar tissue and the resultant cicatricial ectropion.



**Key words:** Laser; Antifibrotic agents; Cicatricial ectropion; Periocular scarring; Ablative fractional resurfacing

**Core tip:** There is a broad range of conservative as well as more invasive treatment modalities for cicatricial ectropion. Ablative lasers can be used alone or in conjunction with nonablative lasers in the treatment of periocular scarring and cicatricial ectropion. Additionally, they may be used to assist the transdermal delivery of antifibrotic agents. This treatment modality, although still uncommonly used to treat periocular scarring, is a promising new technique that offers many advantages. Ophthalmologists may utilize this technique to manage cicatricial ectropion.

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## INTRODUCTION

Cicatricial ectropion presents a formidable clinical challenge; sequelae range from redness, tearing and foreign body sensation to potentially devastating complications, including corneal scarring, ulceration, perforation, and permanent vision loss.

Eyelid eversion is usually secondary to relative shortening of the anterior lamella. A broad range of etiologies

has been reported, but the most common include excision of cutaneous malignancy, prior lower lid blepharoplasty, thermal or chemical burns, and actinic damage in fair-skinned Caucasians[1,2]. Less commonly, cicatrizing skin diseases such as lamellar ichthyosis, scleroderma, neurodermatitis, pyoderma gangrenosum, and Grzybowski-type keratoacanthoma may be implicated[3-5]. Drug related cicatricial changes, including those caused by glaucoma drops and chemotherapeutic agents, generally resolve following discontinuation of the offending agent, but occasionally require additional interventions[6,7]. Tethering within the middle lid lamella, which includes the orbital septum, retractors and preaponeurotic fat, is also a potential cause of cicatricial ectropion, and usually occurs as the result of trauma or prior surgery.

When treating cicatricial ectropion, it is necessary to understand the fundamentals of the wound healing process. Scar formation results from mechanical, chemical or thermal insults to the deep dermis. This initiates a wound-healing cascade that progresses through inflammatory, proliferative and remodeling/maturation phases[8,9]. During the inflammatory phase, platelet activation and degranulation releases cytokines and growth factors that result in the formation of a fibrin clot, which acts as an initial scaffold for repair. This is followed by chemotaxis of macrophages, neutrophils and fibroblasts. Fibroblast growth factor 2 (FGF-2), transforming growth factor (TGF)-β and insulin like growth factor produced by macrophages then induce neocollagenesis. Fibroblasts synthesize extracellular matrix (ECM), which permits vascular ingrowth. Myofibroblasts participate in wound contracture. During the maturation phase, which can take up to two years, the ECM is degraded by matrix metalloproteinases (MMPs) and type Ⅲ collagen is replaced by a more orderly array of type I collagen[8].

There is little systematic documentation in the ophthalmic literature regarding the demographic characteristics of patients with clinically significant cicatricial ectropion. Reviewing the records of 145 patients undergoing skin grafts at the Duke Eye center, Ehrlich *et al*[10] found a male preponderance and a mean age of 75 years. Thirty five percent had undergone prior transcutaneous lower eyelid blepharoplasty, 20% had a history of Mohs reconstruction, 10% a history of facial trauma, and 5% had systemic cicatrizing diseases such as scleroderma. In 45% of patients, however, the etiology was unknown.

## TRADITIONAL SURGICAL MANAGEMENT

Management typically begins with conservative measures such as massage, topical emollients or steroids, and aggressive lubrication of the ocular surface. Even if further interventions are anticipated, it can be helpful to moisten the dry and keratinized palpebral conjunctiva for a few weeks prior to restoring contact with the ocular surface.

Surgical repair is aimed at vertical lengthening of the deficient anterior lamella, but may also incorporate ancillary measures to reduce the likelihood of recurrence, such as horizontal tightening, lid retractor reinsertion, and suborbicularis oculi lift[2,11]. Depending on the etiology of ectropion, lysis of middle lamellar adhesions may also be necessary. Traditional techniques include transposition flaps from the opposing eyelid, full-thickness skin grafts (FTSGs), W- and Z-plasty with scar excision, and island flaps based on the superficial temporal artery[12].

Bipedicle myocutaneous upper to lower eyelid transposition flaps generally offer the best color and texture match. They have been subject to multiple refinements since introduced by Landolt in 1885[11,13]. A bipedicle flap has several distinct advantages over a temporally hinged unbipedicle flap including improved blood supply and improved structural support as it acts as a sling from the upper eyelid[11,13].

FTSGs are also a popular option for anterior lamellar augmentation. Matching of skin color, texture and thickness is critical to optimizing cosmetic and functional outcomes. The suitability of tissues, in descending order, includes the upper eyelid, preauricular area, postauricular area, and supraclavicular region[14]. Lack of suitable donor tissue remains the primary contraindication; burn patients and those with systemic cicatrizing conditions may be poor candidates. Given the prevalence of robust collaterals in the eyelids, necrosis and infection are rare complications. Careful hemostasis and use of postoperative bolsters, however, are necessary to reduce the risk of hematoma formation, which can rapidly devitalize a graft.

Z-plasty is useful for addressing cicatricial ectropion, but is limited to cases resulting from focal scarring. It is typically combined with scar excision or minimization. W-plasty is a related revision technique that creates a regularly irregular wound in lieu of a straight one, lengthening parallel to the original scar. Increased skin tension contributes to further hypertrophic scarring, creating a vicious cycle that can be broken by these revision techniques[9].

## ALTERNATIVE TECHNIQUES

Systemic cicatrizing disease may limit the availability of viable autograft tissues. Some authors report use of groin or even penile foreskin in the setting of limited donor sites[4,15,16]. More radical departures, such as grafting mucus membranes, maternal skin, and even human skin replacements, have been described[15,17,18].

Hyaluronic acid fillers have also been used to treat select cases of cicatricial ectropion. It is thought that the filler volume physically supports the eyelid margin and acts as an injectable tissue expander, stretching the tethered anterior lamella[1]. It may be an attractive alternative in older, debilitated patients and those not desiring further surgical intervention.

## APPLICATION OF LASERS FOR SCAR REVISION AND CICATRICIAL RELEASE

Laser therapy has rapidly evolved into a valuable treatment modality to improve the appearance and physical properties of cutaneous scar tissue throughout the body.

**Table 1 Fitzpatrick sun reactive skin types**

| Skin phototypes | Sunburn | Tan |
|---|---|---|
| Type Ⅰ | Yes | No |
| Type Ⅱ | Yes | Minimal |
| Type Ⅲ | Yes | Yes |
| Type Ⅳ | No | Yes |
| Type Ⅴ | No | Yes |
| Type Ⅵ | No | Yes |

The principles and treatment rationale for laser treatment of scars can also be extended to the treatment of cicatricial ectropion.

### Selection of treatment candidates

Prior to proceeding with laser therapy for scar revision, several factors that are individual to each patient need to be considered. First, the patient's skin type is determined-with a classification scheme such as the Fitzpatrick scale (Table 1)-in order to stratify the patient in terms of appropriate laser settings and possible risks and side effects of laser therapy[19]. Greater skin pigmentation results in increased interference of the energy delivered by the laser, thus decreasing the amount delivered to the targeted hemoglobin and therefore the dermal scar tissue. Additionally, patients with darker skin types are at greater risk of melanin destruction which leads to postoperative skin dyspigmentation[20-22].

Caution should also be taken in patients with inflammatory, autoimmune, or infectious skin disorders. Dermal inflammation of any etiology may interfere with postoperative healing and therefore decrease the overall effectiveness of the laser treatment. Patients may experience exacerbation or dissemination of autoimmune (*e.g.*, vitiligo, lupus) or inflammatory (*e.g.*, psoriasis, eczema) conditions after laser therapy. Additionally, 0.5% to 4.5% of patients undergoing ablative laser treatment can experience exacerbation of disseminated skin infections (*e.g.*, herpes simplex virus, impetigo, mollusum, verruca)[20-22]. It has been recommended that prophylactic oral antiviral agents be administered in patients with a history of perioral herpes simplex one day before treatment and continued one week after treatment[20,22], although most physicians treat patients regardless of history if using ablative therapy.

The patient's current and previous medication usage should also be reviewed prior to initiating laser therapy. Isotretinoin and other common medications may lead to development of hypertrophic scars. Anticoagulants and antiplatelet agents should be discontinued one week prior to treatment to decrease the amount of post-treatment bruising[21].

Additional caution should be exercised in patients who have undergone previous treatments such as chemical peels, dermabrasion, or dermal filler injections[21].

### Selection of laser and application

In general, lasers used for scar tissue remodeling can be divided into two major categories: ablative and nonablative (Table 2)[23,24]. Ablative lasers [*e.g.*, Erbium:yttrium-aluminum-garnet (Er:YAG) 2940 nm, $CO_2$ 10600 nm] have a high affinity for water and causes thermal necrosis as the energy is absorbed by scar tissue. Application of this type of laser also results in an increased level of basic FGF and reduces TGF-β1, which theoretically decreases re-contraction of scars[25,26]. Treatment with this laser induces scar remodeling and improves atrophy, contracture, and texture of existing scar tissue. Commonly experienced side effects after treatment include pain, post-treatment erythema, transient and permanent hyperpigmentation, and infection[26,27]. The Er:YAG laser has a higher affinity for water than the $CO_2$ laser, and therefore patients typically experience less severe side effects[27].

Nonablative lasers [*e.g.*, 532-nm or 1064-nm neodymium:YAG (Nd:YAG), 585-nm pulsed-dye laser (PDL)] are chromophore-selective (*e.g.*, hemoglobin and melanin), and are thus selectively absorbed without inflicting widespread damage to surrounding tissues[27,28]. Application of the 532-nm neodymium YAG laser and 585-nm PDL results in absorption of energy by the hemoglobin, which has an absorption peak of 542-nm, that is present within the scar microvasculature. This results in ischemia, thrombosis, coagulation necrosis, and decreased collagen within the scar. At this wavelength, the laser energy is also selectively absorbed by melanin, which causes decreased scar hyperpigmentation. Additional benefits include decreased proliferation of fibroblasts[29] and deposition of collagen Ⅲ. Similar to ablative lasers, PDL also decreases TGF-β1. Nd:YAG laser treatments also causes suppression of collagen production. Treatment with nonablative lasers results in improvement of scar texture and pliability[29]. Commonly experienced side effects after treatment include post-treatment purpura and skin dyspigmentation[27].

Although there are no standard algorithms for laser treatment of cicatricial ectropion, a general approach similar to that used in treating scar tissue present in other areas of the body may be followed. In general, scar tissue is first treated with a laser that targets the microvascular component of scar tissue, which destroys the vessels and decreases the inflammation.

Next, laser energy that targets water is used to destroy and remodel the abnormal collagen fibers. Previously, ablative lasers were used to vaporize tissues at a consistent and superficial depth. However, these lasers are now typically applied in a fractional pattern, which results in the ablation of deep columns of abnormal scar tissue [microscopic thermal zones (MTZ)] that are intermixed within islands of untreated normal tissue[20]. This not only allows for a quicker recovery through rapid reepithelization and cell migration from the surrounding tissue with retained adnexal structures[30,31], it also changes collagen by modulating interleukin-1, tumor necrosis factor, TGF, heat shock proteins, and MMP. This results in the clearance of damaged collagen and the proliferation, migration, and differentiation of keratinocytes in wounds that result in the formation of new healthy collagen, resulting in more organized scar tissue with physical properties

**Table 2 Common types of ablative and non-ablative lasers**

| | Wavelength | Manufacturer | Product name |
|---|---|---|---|
| Ablative laser | | | |
| $CO_2$ | 10600 nm | Sandstone medical technologies | Matrix LS-40 |
| | | Lumenis | UltraPulse |
| | | Lumenis | AcuPulse |
| Er:YAG | 2940 nm | Focus medical | NaturaLase ER |
| | | Alma lasers gmbh/quantel derma | Burane |
| | | Sandstone medical technologies | Whisper 3-G |
| | | Sciton | Contour TRL |
| | | Syneron and candela | SmoothPeel |
| Combined $CO_2$ Er:YAG laser | 10600 nm/2940 nm | Sandstone medical technologies | Sandstone medical technologies cortex resurfacing work station |
| Nonablative laser | | | |
| Infrared range | | | |
| Pulsed energy | 1319 nm | Sciton | Thermascan |
| Nd:YAG | 1320 nm | CoolTouch | CT3Plus |
| | | Alma lasers | Harmony XL |
| Diode | 1450 nm | Syneron and candela | Smoothbeam |
| Er:Glass | 1540 nm | Alma lasers | ARAMIS |
| Visible range | | | |
| Pulsed dye laser | 585 nm/532 nm | Chromogenex | Regenlite |
| | | Cynosure | V-Star |
| Long pulsed | 532 nm | Laserscope aura | StarPulse |
| | | Lumenis | VersaPulse |

$CO_2$: Carbon dioxide; Er:YAG: Erbium:yttrium-aluminum-garnet; Nd:YAG: Neodymium:yttrium-aluminum-garnet; Er:Glass: Erbium:Glass.

and function that is more comparable to the surrounding healthy tissue[32-34].

An alternative method of treatment using the ablative $CO_2$ laser includes the pinhole method, where multiple small holes are made in regular intervals within the scar tissue. The delivery of focal laser energy results in a softening effect by breaking down the thick and irregular collagen bundles and may promote to more structured deposition of collagen and elastin[35]. Similar to the fractional pattern method, there is also migration of epithelial cells from surrounding viable tissue.

When using laser for the treatment of cicatricial ectropion, one should keep in mind that the eyelid skin is very thin and fragile so treatment density and power need to be greatly reduced[26] to avoid further damage of periorbital skin. In fact, cicatricial ectropion has also been reported as a complication of fractional $CO_2$ laser treatment and it should be used with caution in patients with a history of previous eyelid surgery or limited skin elasticity[22].

## LASER ASSISTED DRUG DELIVERY

In addition to being used alone or in conjunction with nonablative lasers for treatment of cicatricial ectropion, ablative lasers may also be used in the delivery of therapeutic molecules. Although this is not a common treatment for cicatricial ectropion, the application of principles and treatment rationale for treatment of scar tissue present in other areas of the body can be used to guide treatment of periocular scar tissue.

Compared to systemic therapy, transdermal delivery of therapeutic agents has the advantages of directly targeting the affected organ, limitation of systemic toxicity, decreased drug degradation, and bypass of metabolism by the gastrointestinal and hepatic system. In order to achieve effect, the agent must penetrate the epidermis. The main barrier and rate-limiting step to drug penetration into the skin is the stratum corneum of the epidermis, which is composed of hydrophilic corneocytes arranged within lamellar sheets of hydrophobic lipid matrix. Once penetration is achieved, diffusion of the therapeutic agent encounters less resistance through the dermis (which is composed of collagen, glycosaminoglycans, and elastic fibers) and underlying subcutaneous tissue[36,37].

### *Principles of ablative laser use in conjunction with topical therapeutic agents*

Ablative lasers applied in a fractional pattern [*i.e.*, ablative fractional resurfacing (AFR)] can be used to create vertical columns of ablated tissue at various depths. The two main lasers used for this task include the $CO_2$ laser and Er:YAG lasers mentioned previously in this article. The $CO_2$ laser creates a thicker MTZ when compared to the Er:YAG, but for both lasers the end result is the creation of regular strips of MTZs interspersed between areas of untreated skin containing appendageal units[38]. Histological studies of treated tissue have demonstrated MTZs with diameters up to 100 μm and depths up to 300 μm[39], but laser channels can be set to reach depths much greater than this. Therefore, AFR enhances transdermal delivery of therapeutic agents by disrupting the barrier function of the epidermis while allowing for rapid recovery through migration of epithelial cells from the surrounding untreated areas of skin.

The delivery of topical therapeutic agents can be augmented by adjustment of variables such as channel density and depth. Cumulative permeability of different

therapeutic agents has been studied and shows that for a fixed area of skin and fluence, an increase in the number of channels resulted in increased cumulative permeation. However, there was a nonlinear relationship between cumulative permeation and the number of MTZ channels. Within a given dosing time interval, there is a minimum number of channels required to achieve a targeted drug permeation and creating a greater number of channels will not exert a greater clinical effect[40,41].

MTZ channel depth is controlled by adjusting fluence. As expected, a greater fluence results in greater energy delivered per unit area, which results in a greater depth of penetration[40]. Thus, modulation of fluence can be used to target more superficial *vs* deeper areas of the skin. Although one would expect that cumulative permeation is directly proportional to depth of penetration due to increased exposed surface area for absorption, this has not been shown to be true in *in vivo* studies[41,42]. Oni *et al*[42] used a porcine model to demonstrate that serum levels of lidocaine and its metabolite monoethylglycinexylidide did not show a positive correlation with channel depth. At given time intervals, peak levels were significantly higher at a depth of 250 μm compared to 25, 50, and 500 μm. It has been hypothesized that the depth at which vascular plexuses are located within the tissue play a significant role in drug absorption[42]. Therefore, treatment should be tailored to the anatomical locations of vascular plexus contained within different areas of the skin.

Additional factors that may affect topical drug delivery include diffusion area of each drug from the MTZ channel in which it initially penetrated. This would require a calculation of the number and spacing of channels needed to cover any given area. For example, *in vitro* studies showed that methyl 5-aminolevulinate, a sensitizer in photodynamic therapy, diffuses 1.5 mm from each laser channel[38]. However, the distance of diffusion is likely related to physical properties (such as molecular weight, molecular size, and lipophilicity) of the drug molecule itself, and would need to be empirically determined for each therapeutic agent[37,43].

### *Candidate drugs for ablative laser assisted topical delivery*

The use of antifibrotics in the management and treatment of cicatricial ectropion is still in its infancy and not widely practiced. Conceptually, it is a promising treatment option and warrants further investigation. Antifibrotic agents used to treat scar tissue in other areas of the body, such as interferon gamma, interferon alpha, corticosteroids, and vitamin D are theoretically good candidates for AFR assisted topical delivery[36]. Waibel *et al*[44] demonstrated that AFR assisted topical delivery of triamcinolone (TAC) greatly improved texture in hypertrophic cutaneous scars. It is likely that similar effects would be achieved with cicatricial ectropion.

The technique of AFR assisted topical delivery of therapeutic agents also opens a unique opportunity for localized delivery of unstable agents such as proteins. Local immunosuppressive effects have been shown in both *in vitro* and *in vivo* studies to deliver therapeutic antibodies that retained biological activity after delivery into the skin[45].

Additionally, antimetabolites currently used as injectable therapy for periocular scars would be good candidates for AFR assisted topical delivery. Intralesional corticosteroids such as TAC have been used to treat pathological scars since the 1960s. They are thought to disrupt inflammatory cell migration, reduce the nutrient supply to scar tissue through vasoconstriction, and interfere with the metabolic processes of fibroblasts[46]. Typical treatment regimens entail injecting a 10 to 40 mg/mL concentration at 3 to 6 wk intervals for several months or until scar improvement is noted[8,47]. Most studies report significantly improved pliability and scar volume in 50% to 100% of enrolled patients[9,48,49]. Nevertheless, recurrence rates are relatively high, ranging from 9% to 50%, and side effects include hypopigmentation, skin and subcutaneous fat atrophy, telangiectasia, necrosis, and delayed wound healing[8,46].

5-fluorouracil (5-FU) is a pyrimidine nucleotide analogue first injected off-label for scar therapy by Manuskiatti *et al*[48] in 1989[50-52]. It competitively inhibits thymidylate synthase, disrupting DNA synthesis and blocking collagen formation[8,53]. Concentrations of 40 to 50 mg/mL are typically injected at intervals similar to those for intralesional steroids, although some authors use formulations as dilute as 1.4 to 3.5 mg/mL[9,54]. Haurani *et al*[53] reported a 50% reduction in scar volume, still maintained 1 year after the termination of therapy. Fourteen percent of patients had no significant response[53]. 5-FU has a more favorable side-effect profile, with relatively low rates of local erythema, ulceration and transient hyperpigmentation[8,46]. Hematologic derangements, pregnancy, bone marrow suppression and infection are generally considered contraindications, although significant sequelae have not been reported from local injection for scar therapy[8,9,51].

Combining intralesional TAC and 5-FU was superior to either alone in a prospective, double blinded trial[47]. Wang *et al*[46] reported 62.5% efficacy for hypertrophic scar monotherapy and 92% efficacy with combination therapy. TAC is generally mixed with 5-FU in a ratio ranging from 1:3 to 1:9[9,55]. Steroids appear to reduce the inflammation caused by injection of 5-FU, minimizing pain and swelling, and the decreased concentration of TAC significantly reduces the risk of atrophy and hypopigmentation[47].

## CONCLUSION

Interest in new treatment options for the functional and cosmetic sequelae of periocular scars, particularly those causing cicatricial ectropion, has been growing rapidly among ophthalmologists and oculoplastic surgeons. In addition to traditional medical management and surgical repair, ophthalmologists have drawn ideas from the dermatology literature for the treatment of scars, particularly

keloids and hypertrophic scars. This has led to the application of topical agents, injectable metabolites, and the use of ablative and nonablative lasers in the treatment of periocular scar tissue and cicatricial ectropion. Although the combination of therapeutic agents with laser treatments is in its infancy, it is a promising treatment modality for periocular scar tissue.

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