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REVIEW

Corneal Refractive Surgery in Patients with a History of Herpes Simplex Keratitis: A Narrative Review

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Abstract: The incidence of herpes simplex keratitis (HSK) in patients following corneal refractive surgery is higher than in the general population, and several case reports of ocular morbidity in HSK infection following corneal refractive surgery have been published. HSK is listed by the American Academy of Ophthalmology as a relative contraindication to corneal refractive surgery, although specifics have not been further elucidated. This review summarizes the current literature regarding reactivation of HSK following corneal refractive surgery and provides a guideline for considering corneal refractive surgery in a patient with a previous history of HSK. Based on the current literature, we recommend that corneal refractive surgery is appropriate for patients with a history of HSK without multiple recurrences who have had no evidence of disease for at least one year. In addition to a thorough history and physical examination, we also recommend these patients begin 400 mg twice daily of oral acyclovir or valacyclovir 500 mg once daily for two weeks prior to surgery and continue this regimen for at least two weeks postoperatively or while on topical steroids.

Keywords: herpetic keratitis, LASIK, PRK, PTK, herpes prophylaxis, SMILE, HSV, shingles, varicella zoster, cytomegalovirus, CMV

Introduction

Herpes simplex keratitis (HSK) is the most common infectious cause of blindness.[1] Annually, HSK affects approximately one million people globally.[2] In the United States, 500,000 people are affected by HSK annually.[3] While many recover without permanent visual impairment, 15% will develop severe complications such as persistent pain, dry eye, corneal scarring, and vision loss.[4,5] HSK can be further divided anatomically into epithelial, stromal, or endothelial involvement. Epithelial involvement typically causes pain and redness, while stromal and endothelial HSK can cause vision loss.[6] Stromal HSK only represents two percent of the initial HSV ocular presentations but causes 20–61% of recurrent disease.[7] Disease recurrence, a major driving factor for these adverse outcomes, is common. Young et al found that the risk of recurrence of ocular HSV was 27%, 50%, and 57% at one, five, and ten years, respectively, and increased to 38% and 67% at one and five years, respectively, if the initial episode was followed by recurrence.[8] Due to the high risk of complications with recurrence, understanding potential triggers and possible prophylaxis has been the focus of many researchers.

The Herpetic Eye Disease Study (HEDS), one of the largest multicenter randomized control trials studying ocular HSV to date, found that 400 mg of acyclovir twice

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Table 1 Reports of Post-PRK HSK

Study	Number of (+) Eyes	Previous HSV	Time to Dx s/p Surgery	Clinical Presentation	Treatment	Final VA
McDonnell - Case Series[19]	1/4	Yes	4 weeks	Epithelial herpes keratitis	Topical steroids	–
Rao - Case Series[18]	1/139	No	–	–	Topical steroids	–
Wulff - Case Report[21]	1/1	Yes; labialis	1 week	Epithelial defect	Topical acyclovir hourly for 2 weeks	–

Abbreviations: PRK, photorefractive keratectomy; HSK, herpes simplex keratitis; Dx, diagnosis; s/p, status post; HSV, herpes simplex virus; VA, visual acuity.

daily reduced the rate of all types of ocular HSV recurrence to 19% compared to 32% in the placebo group.[9] The HEDS trial also evaluated psychological stress, infection, and exposure to sunlight as potential ocular HSV triggers. Cohen et al did not find any association with recurrence and these potential triggers.[10] However, animal studies suggest that excimer laser keratectomy and laser-assisted in situ keratomileusis (LASIK) may induce reactivation of ocular HSV.[11,12] These data, along with several case reports and case series, are likely the reason that the American Academy of Ophthalmology (AAO) has listed a history of HSV keratitis as a relative contraindication for corneal refractive surgery.[13] However, ocular herpes is a broad diagnosis and could include conjunctivitis, epithelial keratitis, stromal keratitis, endotheliitis, retinitis, uveitis, and blepharitis.[14] Additionally, patients with HSV can benefit from improved visual acuity with negligible or low risk of recurrence if proper steps are taken.[15–17] In this article, we will review all the case reports, animal studies, prospective studies and retrospective studies in the literature of HSV ocular disease following corneal refractive surgery, with an emphasis on LASIK, PRK, and SMILE. Additionally, we will outline our preferred practice pattern for identifying patients who can safely undergo surgery.

Methods

A literature search of PubMed, AGRIS, Asian Digital Library, and Google Scholar from 1974–2020 was performed using search terms such as herpetic keratitis, human herpes virus, cytomegalovirus, CMV, varicella zoster, VZV, herpes zoster ophthalmicus, refractive surgery, excimer laser, *PTK, PRK, SMILE*, and *LASIK*. In all, the literature review yielded 24 case reports, five prospective case series, two retrospective case series, one uncontrolled trial, and five animal studies. Articles were written mainly in English; however, three case reports in Spanish, Portuguese, and Turkish were also included.

Post-PRK Herpetic Ocular Disease

A review of the literature yielded three animal studies, two prospective case series, one case report, and one retrospective study that suggest excimer laser photorefractive keratectomy (PRK) as a trigger of HSV keratitis.[11,18–23] A summary of the case series and case report findings of post-PRK HSK can be found in Table 1. Within the animal studies, Pepose et al found that excimer laser pulses, corneal epithelial scraping, and combined corneal epithelial scraping all caused increased HSV shedding in mice.[22] Dhaliwal et al demonstrated that epithelial scraping and excimer laser pulses caused a 45% reactivation rate versus only 5.6% HSV recurrence in control rabbits.[11] Additionally, according to Dr. Asbell's animal studies, it would appear that the excimer laser plays a major and specific role in the reactivation of HSK. Asbell demonstrated that de-epithelialization alone did not reactivate HSV in rabbits but that de-epithelialization coupled with excimer laser resulted in 66.67% HSV keratitis reactivation rate providing strong evidence that the excimer laser was the trigger for recurrence.[23] It has been long established that B wavelength ultra-violet light (UVB) can trigger HSV recurrence in humans.[24] Asbell's study was the first to suggest conclusively that the 193 nm UVC light could also reactivate HSV possibly explaining the reactivation of HSK seen in radial keratectomy (RK), PRK, PTK, and LASIK.[20,23,25]

In humans, the data have been less clear. Nagy et al found after reviewing 13,200 post-PRK eyes that the incidence of post-PRK HSV keratitis was 0.14% (19 of 13,200), much higher than the incidence of 0.0315% in the general population.[20,26] Seventy-eight percent of patients presented within 15 weeks of surgery and none of the patients had documented HSV keratitis prior to surgery.[20] Two case

series and one case report were reported in the literature.[18,19,21] Of the two case series only two out of 143 eyes that had undergone PRK presented with HSK following surgery.[18,19] McDonnell et al's study was the only report of a patient with a positive herpetic ocular disease history before PRK.[19] Wulff et al did document that their patient had herpes labialis; however, non-ocular herpetic infections are not contraindications to corneal refractive surgery.[21]

Post-PTK Herpetic Ocular Disease

Phototherapeutic keratectomy (PTK) uses the same excimer laser as PRK and is indicated in patients with corneal opacities, irregularities, or any corneal refractive error that is caused by trauma, previous surgery, or disease.[27] As recurrent HSK commonly causes scarring, 86% (12/14) of the patients who developed HSK post-PTK had previous ocular herpetic disease in the seven case reports found in the literature.[18,28–34] A summary of the case reports can be found in Table 2. Interestingly, at least five of the 14 reported cases involved reactivation of stromal keratitis. This reactivation is significant as the HEDS trial found that patients with a history of ocular herpetic disease, but not HSV stromal keratitis, only had recurrence rates of 3% compared to recurrence rates of 28% in patients with a history of HSV stromal keratitis.[35] In the longest epidemiologic study to date, Young et al found that most adverse outcomes, including scarring, did not occur until after, on average, four recurrences.[8] Additionally, disease recurrence is a strong predictor of subsequent recurrences.[8] Since the patients in these studies were undergoing PTK for scarring due to HSK, they were already at high risk of recurrence even without surgery. Nevertheless, Deai et al did find that PTK was sufficient to cause levels of viral shedding seen in reactivated herpetic ocular disease in one HSV positive patient.[33] If PTK and lasers in other corneal refractive procedures do cause increased viral shedding, it is significant as Perng et al found that high viral loads in tears precede recurrent HSK in rabbits.[36]

Post-LASIK Herpetic Ocular Disease

Eleven case reports and one retrospective study discussed post-LASIK ocular herpes in 19 patients.[25,30,37–48] A summary of the findings of each paper can be found in Table 3. Of note, the presentation of HSK ranged from one day post-LASIK to 28 months, with the median being four weeks. Of the infections, 37% (7/19) were presumed epithelial HSK, 32% (6/19) stromal HSK, 11% (2/19) disciform endotheliitis, 16% (3/19) keratouveitis, and 5 % (1/19) polymicrobial. Where reported, only 56% (10/19) of patients were previously diagnosed with HSV infection, and only three patients had previous ocular manifestations of the

Table 2 Reports of Post-PTK HSK

Study	Previous HSV	Time to Dx s/p Surgery	Clinical Presentation	Treatment	Final VA
Fagerholm[28]	Yes	–	Case series with 5/20 eyes developing HSK reactivation	Topical steroids, topical acyclovir	Decreased
Tervo[29]	Yes	8 days	Stromal herpes keratitis	–	–
Lu[30]	No	3 weeks	Epithelial herpes keratitis	Topical acyclovir 5x/day	–
Vrabec1[31]	Yes	12 weeks	Stromal herpes keratitis	Topical steroids	Decreased
Vrabec2[31]	Unclear	12 weeks	Epithelial herpes keratitis	Topical steroids	Unchanged
Vrabec3[31]	Yes	16 weeks	Epithelial herpes keratitis	Topical steroids, topical trifluridine	Decreased
Vrabec1[32]	Yes	18 months	Epithelial herpes keratitis	Topical steroids, topical trifluridine	Decreased
Starr1[34]	Yes	16 weeks	Herpetic keratouveitis	Topical steroids, oral acyclovir, topical trifluridine	Decreased
Starr2[34]	Yes	14 months	Herpetic keratouveitis	Topical steroids, oral acyclovir, topical trifluridine	Decreased
Starr3[34]	Yes	17 months	Herpetic keratouveitis	Topical steroids, oral acyclovir, topical trifluridine	Decreased

Abbreviations: PTK, phototherapeutic keratectomy; HSK, herpes simplex keratitis; Dx, diagnosis; s/p, status post; VA, visual acuity.

Table 3 Reports of Post-LASIK HSK

Study	Previous Infection	Time to Dx s/p Surgery	Clinical Presentation	Treatment	Final VA
Davidorf[44]	Yes; ocular	1 day	Epithelial dendrites	Trifluridine every 2 hours while awake for 1 week, famciclovir 375 mg 3x/day for 2 weeks, artificial tears	20/20
Perry[42]	Yes; ocular	10 days	Cornea edema, corneal perforation	Oral acyclovir 2x/day, prednisolone 1% 4x/day, ofloxacin 4x/day, cyclosporine A 0.5%, lamellar keratoplasty	20/50
Levy1[46]	Yes; labialis	6 weeks	Corneal edema, KP, epithelial dendrites	Topical steroids 8x/day, acyclovir 400 mg 5x/day, topical acyclovir 5x/day	20/30
Levy2[46]	Yes; ocular	2 years	Pain, stromal edema, DM folds, epithelial dendrites	Oral valacyclovir 3 g 3x/day, dexamethasone 4x/day, topical acyclovir 5x/day	20/20
Lu[30]	No	4 weeks	Pain, blurred vision, epithelial dendrites	Topical acyclovir 5x/day, oral acyclovir 200 mg 5x/day for 10 days	20/20
Kamburoglu[45]	No	8 days	Epithelial ulcer, stromal infiltrate, KP, corneal edema	Topical steroids hourly, topical acyclovir 5x/day, oral valacyclovir 400 mg 5x/day for 2 months	–
Moshirfar1[25]	No	1 day	Epithelial dendrites, hypopyon, disciform endotheliitis	Topical trifluridine, oral valacyclovir 500 mg 2–3x/day, prednisolone 1%, systemic corticosteroids	20/200
Moshirfar2[25]	No	21 weeks	Epithelial dendrites	Topical trifluridine, oral valacyclovir 500 mg 2–3x/day, prednisolone 1%	20/40
Moshirfar3[25]	No	25 weeks	Epithelial dendrites	Topical trifluridine, oral valacyclovir 500 mg 2–3x/day, prednisolone 1%	20/30
Moshirfar4[25]	No	1 week	Epithelial dendrites	Topical trifluridine, oral valacyclovir 500 mg 2–3x/day, prednisolone 1%	20/40
Moshirfar5[25]	No	2 weeks	Epithelial dendrites	Topical trifluridine, oral valacyclovir 500 mg 2–3x/day, prednisolone 1%	20/30
Jain[39]	Yes; ocular	5 weeks	Corneal edema, KP, disciform endotheliitis	Oral acyclovir 400 mg 5x/day, prednisolone 1%	20/30
Gomez[43]	Yes; labialis	1 day	Epithelial dendrites	Topical acyclovir 5x/day	–
Arora[41]	No	2 weeks	Hypopyon, corneal edema, KP, DM folds, stromal infiltrates, flap necrosis	Topical steroids, oral valacyclovir 1000 mg 2x/day	20/30
Srirampur[47]	Yes; ocular	20 weeks	Pain, redness, photophobia, ring-like infiltrate under flap and scarring	Oral acyclovir 400 mg 5x/day, prednisolone 1% 4x/day, atropine 3x/day	20/20
Gupta[48]	–	–	Polymicrobial keratitis (*S. epidermidis, F. solani, HSV*)	Keratoplasty	20/40
Goto[37]	Yes; ocular	10 months	Herpetic keratouveitis	Topical betamethasone, topical acyclovir	20/13
Nakano[38]	Yes; ocular	28 months	Herpetic keratouveitis	Oral acyclovir 2 g, oral prednisone 60 mg, prednisolone 1%	20/20
Orucoglu[40]	Yes; ocular	–	Disciform endotheliitis	Antiviral, topical dexamethasone	–

Abbreviations: LASIK, laser-assisted in situ keratomileusis; HSK, herpes simplex keratitis; Dx, diagnosis; s/p, status post; KP, keratic precipitate; DM, Descemet membrane; HSV, herpes simplex virus.

disease. While most patients recovered vision to 20/40 or better, one patient had a final vision of 20/200.[25]

Post-SMILE Herpetic Ocular Disease

Small-incision lenticule extraction (SMILE) uses a femtosecond laser to create small corneal incisions circumventing the need to create a flap, as in LASIK.[49] SMILE was first performed and pioneered by Sekundo et al. There has only been one reported case of possible HSK post-SMILE.[50,51] The patient presented three days after undergoing SMILE with decreased vision, pain, and decreased corneal sensitivity. Notably, she had no signs of ulceration or discharge; fungal and bacterial cultures were negative. Idiopathic noninfectious lamellar keratitis was the most likely diagnosis; however, herpes keratitis could not be ruled out due to decreased corneal sensation, stromal involvement, and appearance on OCT. She was treated with dexamethasone 4 mg subconjunctival injections and valacyclovir 3 g daily for 15 days.[51]

Post Refractive Surgery Reactivation of Other Human Herpes Viruses

While herpes simplex virus 1 is the most common cause of ocular disease, other herpes viruses such as herpes simplex virus 2, cytomegalovirus (CMV or HHV5), varicella zoster virus (VZV or HHV3), and Epstein-Barr virus (EBV or HHV4) are all known to cause ocular pathology.[52] However, only three case studies were found in the literature demonstrating reactivation of CMV and VZV after corneal refractive surgery.[53–55] The reactivation of VZV occurred two months after LASIK, with the patient making a full recovery after treatment with valacyclovir 500 mg twice daily and topical acyclovir twice daily.[54] In a separate case report, Kaufman et al reported a patient with a previous corneal scar due to herpes zoster ophthalmicus (HZO) who underwent PTK, PRK, and LASIK without reactivation.[56] HZO, the reactivation of VZV in the ophthalmic division of the trigeminal nerve, most commonly presents as keratitis, conjunctivitis, and uveitis. Similar to HSK, studies report high recurrence rates ranging from 31–51% in the first six years following primary infection.[57,58] Treatment of HZO is started within 72 hours of onset with 1000 mg of valacyclovir three times per day, acyclovir 800 mg five times per day, or famciclovir 500 mg three times per day for one week.[59] Vaccination is the preferred primary prevention and some reports suggest the efficacy of oral acyclovir for secondary prophylaxis.[60,61]

The activation of CMV corneal endotheliitis occurred three weeks post-LASIK in a patient who presented with blurred vision and increased intraocular pressure (IOP) of 32 mmHg. Anterior uveitis was treated with topical dexamethasone 0.1% and moxifloxacin 0.5%, which then resolved after two weeks. The patient subsequently presented twice more before the diagnosis of CMV endotheliitis was made and was successfully treated with ketorolac tromethamine 0.5% four times a day and ganciclovir 0.15% five times a day. The patient was offered oral acyclovir which was declined due to economic reasons.[53] The patient had no known history of CMV and activation was believed to be due to local immunosuppression secondary to the steroids received, similar to cases seen after cataract surgery and corneal transplantation.[53,62,63] A similar case reported by Bacsal et al discussed a patient with anterior uveitis and increased IOP two months after LASIK. The patient was eventually diagnosed with CMV uveitis and treated with oral valganciclovir and topical rimexolone for 10 weeks.[55] Although CMV retinitis is the most commonly recognized ocular manifestation, CMV corneal endotheliitis, and uveitis are the most common ocular manifestations in immunocompetent patients.[64] Treatment of CMV endotheliitis is valganciclovir 900 mg twice daily until the eye becomes quiet and then can be decreased to once per day for one year. Blood counts, liver enzymes, and creatinine should be measured prior to prescription as valganciclovir can cause bone marrow depression, hepatotoxicity, and renal toxicity. Additionally, topical corticosteroids are used to manage inflammation and antiglaucoma medications can be used for increased IOP.[65]

One case of Kaposi's sarcoma was reported in the literature in a patient who had LASIK four years before who presented with bilateral subconjunctival hemorrhagic lesions. However, the patient was discovered to be HIV positive without treatment and this was believed to be the cause of the disease, not previous corneal refractive surgery.[66] One possible case of EBV infection following PTK was reported in the literature. The patient presented with glare, photophobia, and subepithelial opacities and was treated with fluorometholone drops for presumed epidemic keratoconjunctivitis (EKC); however, EBV could not be ruled out.[67]

Corneal Refractive Surgery HSV Prophylaxis

While there is strong evidence to suggest that oral acyclovir reduces the recurrence of ocular HSV, there are few studies that discuss prophylaxis prior to refractive surgery. In our literature review, we found only three studies and

two animal models that had examined prophylactic treatment as a method to prevent HSV reactivation.[15–17,23,68] Their results are summarized in Table 4. As evidenced, treatment regimens varied widely regarding dosing as well as pre- and postoperative treatment course duration. However, all of the studies used oral acyclovir or valacyclovir as a prophylactic agent. In the Dhaliwal et al animal model, they demonstrated that acyclovir reduced HSV-1 positive eyes from 35.3% of the control group to 6.2% of the treatment group after LASIK.[68] Asbell reported even stronger evidence for prophylactic use of valacyclovir with no reactivation in her animal model.[23] Although the human studies involved different antivirals (valacyclovir, oral and topical acyclovir, famciclovir) and dosing protocols (oral acyclovir 800 TID, valacyclovir 500 mg BID), all studies showed no reactivation .[15–17]

Regarding other ocular surgeries, there is little consensus for prophylactic dosing, choice of pharmacologic agent, and length of treatment. Sykakis et al found that while 92.5% of cataract surgeons prescribe oral acyclovir perioperatively for patients with prior HSV keratitis, there was little consensus on dosage or timing.[69] Yu et al recently published a prospective case series studying the effects of high dose acyclovir 800 mg twice per day

Table 4 Prophylactic HSV Treatment - Human and Animal Trials

Study	Study Design	Previous Infection	Number of Subjects/ Patients	Treatment	Clinical Outcome
Asbell[23]	RCT—Animal model	Inoculation	Group 1: 8	Group 1: De-epithelialization, IP saline for 14 days	Group 1: 0% reactivation
			Group 2: 15	Group 2: De-epithelialization, laser, saline for 14 days	Group 2: 66.67% reactivation
			Group 3: 8	Group 3: De-epithelialization, laser, valacyclovir 50 mg/kg/day for 14 days	Group 3: 50.00% reactivation
			Group 4: 6	Group 4: De-epithelialization, laser, valacyclovir 100 mg/kg/day for 14 days	Group 4: 16.67% reactivation
			Group 5: 6	Group 5: De-epithelialization, laser, valacyclovir 150 mg/kg/day for 14 days	Group 5: 0% reactivation
Dhaliwal[68]	RCT – Animal model	Inoculation		Valacyclovir postop:	
			Group 1: 16	Group 1: 100 mg/kg/day for 7 days	Group 1: 6.2% reactivation
			Group 2: 16	Group 2: 200 mg/kg/day for 7 days	Group 2: 6.2% reactivation
			Control: 17	Control postop: saline for 7 days	Control: 35.3% reactivation
Jarade[15]	Prospective, interventional case series	HSK	3	Oral acyclovir 800 mg 3x/day 1 week preoperatively, 800 mg 3x/day and topical acyclovir at bedtime 2 weeks postoperatively	No recurrence of HSK Preoperative BCVA: 20/25, 20/50, 20/120 Postoperative: 20/20, 20/20, 20/50
De Rojas Silva[16]	Uncontrolled trial	HSK	5	Valacyclovir 500 mg 2x/day for 1 week preoperatively and 2 weeks postoperatively, 0.3% ofloxacin 4x/day for 5 days, topical acyclovir 1x/day for 2 weeks	No recurrence of HSK. Mean preoperative SE: −3.2 diopters (−1.75 to −6 D). Postoperative UCVA 20/20-25
De Rojas Silva[17]	Retrospective case series	HSK	13	Valacyclovir, oral acyclovir, famciclovir, and topical acyclovir started 2 days to 2 weeks prior to surgery, and regimens discontinued 5 days to 5 months postop	No recurrence of HSK. Mean preoperative SE: −2.46 diopters (−11 to +6.25 D). Mean postoperative SE: −0.12 (−1.25 to +1.25 D)

Abbreviations: HSV, herpes simplex virus; RCT, randomized control trial; IP, intraperitoneal; HSK, herpes simplex virus keratitis; BCVA, best corrected visual acuity; SE, standard error; D, diopter; UCVA, uncorrected visual acuity.

beginning three months prior to keratoplasty and then increased to five times per day for three months following surgery. The study showed low recurrence rates in the grafts (7.8%) especially compared to previous studies done by Goldblum et al (15.8%) and Wu et al (37.7%).[70–72] Nevertheless, such long treatment duration of acyclovir must be weighed against increasing HSV resistance.[73] Van Velzen et al reported resistance rates greater than 28% in patients who had used acyclovir prophylactically for more than one year.[74] Additionally, Rousseau et al found that 83% of patients with relapsing HSK despite appropriate prophylaxis had viruses that were genetically resistant to acyclovir.[75] As thymidine kinase is believed to confer resistance to acyclovir, cross-resistance can also be seen with ganciclovir.[76] In these patients, foscarnet, cidofovir, and trifluridine can be considered to treat active infection.[75,77,78]

Pathogenesis of Post Refractive Surgery HSK

Two large retrospective studies that each reviewed over 10,000 eyes found that the incidence of HSK is far greater post-PRK (0.14% vs 0.031%) and post-LASIK (0.048% vs 0.031%) when compared to the general population.[20,25,26] Although the exact mechanism is unknown, it is theorized that immunosuppression from topical steroids and neuronal cell death caused by the excimer laser and surgical trauma as well as immunosuppression caused by topical steroids lead to reactivation.[23,79,80]

Authors' Guidelines

Initial Evaluation

Ask specifically about general and ocular HSV infections. While primary ocular HSV infections can occur, they are rare and usually present early in life.[4] Typically, infections arise from the activation of a dormant infection in the trigeminal ganglion after a non-ocular infection.[5] In addition to affecting the cornea, HSV can affect all other major ocular tissues, including the conjunctiva, lids, uveal tract, and the retina.[81] Thus, it is important to ask which part of the eye was affected. De Rojas et al demonstrated that even without prophylaxis, no herpetic reactivation occurs with previous HSV blepharitis.[17]

Serologic testing prior to corneal refractive surgery is not recommended. In the US, primary infection with HSV-1 and HSV-2 occurs in the vast majority of individuals by the age of 60, and many of these infections are asymptomatic.[82] Additionally, HSV-1 DNA has been isolated in the tears and the trigeminal nerve ganglia of individuals who have no reported history of ocular HSV-1 disease.[83] Prophylaxis is not recommended for these patients. However, within our review of the case reports, 33% (12/36) of patients who presented with HSV keratitis post-refractive surgery had no known prior HSV infection.

Surgery is not recommended for patients with multiple recurrences. Young et al reported that the risk of subsequent recurrence increases with each HSK reactivation; therefore, we suggest that corneal refractive surgeons exercise extreme caution when considering elective surgery on patients with previous HSK and two or more recurrences.

Delay surgery at least one year from most recent HSV recurrence. If the patient does have a positive history of HSK, they should be asked how long it has been since their most recent recurrence. In the two small studies reporting no HSK reactivation post-LASIK, only patients who did not report recurrence within one year prior to surgery were included.[15,16]

Physical Examination

Patients with no corneal haze, nummular keratopathy, or signs of neovascularization can be considered candidates for corneal refractive surgery. Examination should include visual acuity, a comprehensive external examination of the eyelids, corneal sensation testing, and slit-lamp examination. Patients with a history or suspected history of HSK should have corneal sensation testing because sensation is often impaired post-infection. Slit-lamp examination should include evaluation for stromal haze, nummular keratopathy, pannus, and neovascularization as these can be signs of previous viral infection. Additionally, attention should be directed toward any endothelial changes as possible evidence of endotheliitis.[2,84]

Prophylaxis

For LASIK, oral acyclovir 400 mg twice daily or valacyclovir 500 mg once daily for two weeks before and continued for 2 weeks after surgery is suggested. For PRK, SMILE, and other corneal refractive procedures, begin oral acyclovir 400 mg twice daily or valacyclovir 500 mg once daily for two weeks before surgery and continue course postoperatively until cessation of topical steroids. Without the benefit of randomized control trials or consensus within the scientific literature, we recommend the dosing suggested by HEDS trial for HSK prophylaxis. We recommend starting the prophylaxis

two weeks prior to surgery as supported by the prospective study of De Rojas et al wherein no recurrence was seen.[16] Although intraocular corticosteroid injections have been shown to cause HSK reactivation, the role of topical steroid drops is less clear.[85] Still, there is a theoretical risk for HSK reactivation with the use of topical steroids and, thus, for PRK and SMILE, we suggest continuing acyclovir or valacyclovir concurrently with steroid drops. If patient compliance is a concern, Miserocchi et al reported no difference in HSK recurrence between acyclovir or valacyclovir.[86] Thus, valacyclovir 500 mg once daily is an appropriate choice for prophylaxis. If there is a concern for resistance due to previously failed prophylaxis or prolonged disease course despite treatment, we recommend that these patients be strongly counseled to avoid corneal refractive surgery due to the higher risk of HSK reactivation.

Conclusion

Although rare, HSK reactivation can occur following corneal refractive procedures. This is significant as recurrence leads to worse visual outcomes. Nevertheless, not all patients with previous ocular HSV should be precluded from surgery. Patients with previous HSK who have been disease-free for at least one year, have no signs of active infection, and are managed prophylactically may be considered for corneal refractive surgery. As with every operation, each patient should be counseled on the risks and benefits of the procedure. Still, the literature regarding HSK prophylaxis before and after surgery is lacking. With more animal studies and randomized control trials, ophthalmologists will be better able to counsel their patients regarding operations that could significantly improve visual acuity.

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Author Contributions

All authors made substantial contributions to conception and design as well as analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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