Infectious Ulcerative Keratitis Following Retinopathy of Prematurity Treatment

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ABSTRACT

Purpose: To report the complication of infectious ulcerative keratitis after laser photocoagulation and pars plana vitrectomy (PPV) for retinopathy of prematurity (ROP).

Methods: A retrospective chart review of infants treated for ROP with plus disease between 2004 and 2013 at University Hospital, Newark, New Jersey.

Results: Of the 110 eyes (55 patients) that underwent treatment for ROP, 8 (7.27%) eyes were noted to develop infectious ulcerative keratitis in 4 neonates (4 eyes after laser photocoagulation and 4 eyes after PPV). All 8 eyes that developed ulcerative keratitis had a preceding corneal epithelial defect followed by corneal stromal haze. Seven of 8 eyes developed epithelial defect within 8 days of the procedure. All epithelial defects progressed to ulcerative keratitis within 7 days. A total of 10 (9.1%) eyes developed postoperative epithelial defects, and 8 (80%) of these eyes were ultimately diagnosed as having ulcerative keratitis. Four (4.08%) of 98 eyes treated with laser photocoagulation alone developed infective ulcerative keratitis, compared to 4 (33.33%) of 12 eyes treated with PPV. Because keratitis healed, corneal opacification ensued and covered 10% to 90% of the corneal surface area. Five of the 8 eyes had positive culture of corneal scrapings: 2 grew coagulase-negative Staphylococcus and Stenotrophomonas; 1 grew coagulase-negative Staphylococcus; 1 grew Streptococcus viridans, and 1 grew Staphylococcus hominis, Streptococcus mitis, and Streptococcus viridans. All 8 eyes were treated with antibiotic eye drops.

Conclusions: Infectious ulcerative keratitis developed in a small, but significant, percentage of patients undergoing treatment for ROP. Postoperative corneal epithelial defects with subsequent corneal haze appear to be involved in the progression to ulcerative keratitis.

INTRODUCTION

Retinopathy of prematurity (ROP) is a major cause of blindness in industrialized and non-industrialized societies, despite recent innovations in intervention. ROP was first described in the 1940s, when its association with premature birth was established. Laser photocoagulation emerged as the gold standard treatment for ROP with plus disease after clinical trials demonstrated its superiority to the previously established treatment, retinal cryotherapy. For advanced-stage ROP (partial or complete retinal detachment), pars plana vitrectomy (PPV) may be indicated. With some studies reporting that ROP occurs in approximately 65% of premature newborns, ROP has been described as a “third epidemic” worldwide.
Although laser photocoagulation has been effective, complications are well documented in the literature and include anterior segment ischemia, corneal opacification, hyphema, iris burns, vitreous hemorrhage, and cataract. The extant literature regarding corneal infection following posterior segment procedures for ROP, including laser photocoagulation and PPV, is scarce.

This study reports infectious ulcerative keratitis as an infrequent but significant complication of treatment procedures (laser photocoagulation and PPV) in preterm infants treated for ROP. Infectious ulcerative keratitis is a rare condition in infants. A bimodal distribution is typically observed in adults with this condition. The first group, those younger than 30 years, usually has a history of contact lens wear or ocular trauma. The second group includes individuals older than 50 years, who typically sustain corneal trauma after eye surgery. To our knowledge, infectious ulcerative keratitis has not been reported as a complication of ROP treatment.

**PATIENTS AND METHODS**

A retrospective chart review of 55 infants treated for ROP between 2004 and 2013 at University Hospital, Newark, New Jersey, was undertaken. Patients were observed through their inpatient admission and outpatient follow-up. A total of 110 eyes that underwent laser photocoagulation were included in the study. All of the treated eyes were staged according to the International Classification of Retinopathy of Prematurity. Data collected on the patients included gestational age, birth weight, intubation/oxygen assistance, medications given prior to intervention, age at diagnosis of ROP, International Classification of Retinopathy of Prematurity stage, retinal zone involved, postoperative eye drops, age at laser treatment, presence of corneal epithelial defect, presence of corneal haze, presence of infectious ulcerative keratitis, organisms cultured, and management of the keratitis. Data were collected from all patients for every follow-up visit.

**RESULTS**

Of the 110 eyes that underwent treatment for ROP, a total of 8 (7.27%) eyes of 4 patients developed infectious ulcerative keratitis. Four (4.08%) of 98 eyes treated with laser photocoagulation alone developed infective ulcerative keratitis, compared to 4 (33.33%) of 12 eyes treated with PPV.

All 8 cases of ulcerative keratitis were first preceded by a postoperative corneal epithelial defect, followed by a stromal haze. After their first procedure for ROP, 7 of the 8 eyes were noted to have epithelial defects within 8 days (range: 1 to 14 days). A total of 10 (9.1%) of 110 eyes developed postoperative epithelial defects, and 8 (80%) of 10 of these eyes progressed to infectious ulcerative keratitis. Because the keratitis healed, dense corneal opacification was noted in these eyes, spanning 10% to 90% of the corneal surface area.

Seven of the 8 eyes underwent conjunctival swab cultures and corneal scrapings. Five (62%) of these 8 eyes had positive cultures of the corneal scrapings (Table 1). On diagnosis of the keratitis, all eyes were treated with multiple antibiotic drops. Each case is described briefly below.

**Patient 1**

Patient 1 was a male infant at 26 weeks of gestation with a birth weight of 384 g who developed bilateral stage 3, zone II ROP with plus disease. The patient underwent laser photocoagulation at 35 weeks post-menstrual age and responded well with ROP regression. The patient was given cyclopentolate and tobramycin drops following laser photocoagulation. Epithelial defects with concomitant corneal haze were noted at 8 days (right eye) and 5 days (left eye) after laser treatment at the first follow-up visit. At this point, tobramycin was discontinued and moxifloxacin and trimethoprim/polymyxin B eye drops were administered. Three days later, on identification of ulcerative keratitis, the antibiotic regimen was left unchanged. Twenty days (right eye) and 38 days (left eye) after their appearance, both eyes were noted to be healing, at which point corneal opacification was noted. During the next 2 months of hospitalization, the corneal opacification began to improve progressively. At this point, the patient was transferred to another institution and lost to follow-up. Positive culture results were not obtained in this patient.

**Patient 2**

Patient 2 was a male infant at 24 weeks of gestation with a birth weight of 695 g who underwent bilateral PPV for stage 4 disease, and was administered levofloxacin, prednisolone, and cyclopentolate drops postoperatively. Bilateral epithelial defects were noted 14 days (right eye) and 8
days (left eye) postoperatively, respectively. At this point, ophthalmic bacitracin ointment was added, and levofloxacin was discontinued. Over the next several days, corneal haze developed and subsequently progressed to bilateral infectious ulcerative keratitis. Cultures of corneal scrapings were performed and were positive for *Staphylococcus viridans* on one occasion in the right eye. The patient was given fortified vancomycin and fortified gentamicin, and all other drops were discontinued. Two weeks later, both eyes with keratitis began to improve, and corneal opacification was noted. The keratitis continued to improve during the hospital stay, and the patient was released with healing bilateral ulcerative keratitis, but with persistent epithelial defects. After 10.5 months of follow-up, the patient’s right eye underwent a successful allograft using the clearer left cornea as the donor (visual potential of the left eye was thought to be extremely poor) and transplanting the opaque right cornea to the left eye, and the graft remained clear at the 3-year follow-up.\textsuperscript{15}

### Patient 3

Patient 3 was a female infant at 22 weeks of gestation with a birth weight of 441 g who had undergone bilateral intravitreal bevacizumab and ranibizumab injections for posterior aggressive zone I ROP with plus disease, and subsequently underwent laser treatment at 35 weeks (postmenstrual age) (3 weeks after the ranibizumab injection). She was administered moxifloxacin and cyclopentolate postoperatively. The patient was noted to have bilateral epithelial defects and corneal haze 8 days after laser treatment, with rapid progression to infectious ulcerative keratitis within 1 day. On diagnosis of the ulcerative keratitis, the patient was administered tobramycin and fortified vancomycin. Fortified tobramycin switched to ceftriaxone, then moxifloxacin, then ofloxacin. The keratitis was noted to be improving bilaterally, with onset of a corneal opacification 3 weeks later. At this point, the drops were changed to fortified

### TABLE 1

**8 Eyes With Corneal Ulcers After ROP Treatment**

<table>
<thead>
<tr>
<th>Eye</th>
<th>Procedure\textsuperscript{a}</th>
<th>Topical Antibiotics for Ulcer</th>
<th>Duration of Ulcer Before Healing\textsuperscript{a}</th>
<th>Corneal Culture Scraping Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 OD</td>
<td>Laser</td>
<td>Moxifloxacin, trimethoprim/polymyxin B</td>
<td>20 days</td>
<td>Culture not taken</td>
</tr>
<tr>
<td>1 OS</td>
<td>Laser</td>
<td>Moxifloxacin, trimethoprim/polymyxin B</td>
<td>38 days</td>
<td>Culture and Gram-stain negative</td>
</tr>
<tr>
<td>2 OD</td>
<td>PPV</td>
<td>Fortified vancomycin, fortified gentamycin</td>
<td>15 days</td>
<td><em>Staphylococcus viridans</em></td>
</tr>
<tr>
<td>2 OS</td>
<td>PPV</td>
<td>Fortified vancomycin, fortified gentamycin</td>
<td>15 days</td>
<td>Gram stain: G+ cocci, negative culture</td>
</tr>
<tr>
<td>3 OD</td>
<td>Laser</td>
<td>Tobramycin, fortified vancomycin (initially), followed by trimethoprim/polymyxin B and moxifloxacin</td>
<td>27 days</td>
<td>Coagulase – <em>Staphylococcus, Stenotrophomonas</em></td>
</tr>
<tr>
<td>3 OS</td>
<td>Laser</td>
<td>Tobramycin, fortified vancomycin (initially), followed by trimethoprim/polymyxin B and moxifloxacin</td>
<td>27 days</td>
<td>Coagulase – <em>Staphylococcus, Stenotrophomonas</em></td>
</tr>
<tr>
<td>4 OD</td>
<td>PPV</td>
<td>Fortified tobramycin and fortified vancomycin. Fortified tobramycin switched to ceftriaxone, then moxifloxacin, then ofloxacin</td>
<td>16 days</td>
<td>Coagulase - <em>Staphylococcus</em></td>
</tr>
<tr>
<td>4 OS</td>
<td>PPV</td>
<td>Fortified tobramycin and fortified vancomycin. Fortified tobramycin switched to ceftriaxone, then moxifloxacin, then ofloxacin</td>
<td>16 days</td>
<td><em>Staphylococcus hominis, Streptococcus mitis, Streptococcus viridans</em></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Because patients were not seen on a daily basis, epithelial defects may have emerged prior to when they were diagnosed.

\textsuperscript{b}At the point where the infectious ulcer was noted to be healing and deemed not infectious, a corneal stromal opacification was noted, and prednisolone drops were administered.

ROP = retinopathy of prematurity; OD = right eye; OS = left eye; PPV = pars plana vitrectomy
ceftazidime and levofloxacin, and prednisolone was added. One month later, bilateral corneal opacities remained. At this point, the patient’s family moved out of state, and continued follow-up with an outside corneal specialist to monitor keratitis.

**Patient 4**

Patient 4 was a male infant at 25 weeks of gestation with a birth weight of 750 g who underwent bilateral PPV for bilateral stage 4, zone III ROP with plus disease. After PPV, the patient was given tobramycin, prednisolone, and cyclopentolate drops. Bilateral epithelial defects with stromal haze (and no other anterior ischemic signs) were noted the following day, at which point no change was made to the topical drop regimen. Infectious ulcerative keratitis was diagnosed by the corneal specialist 1 day later, prednisolone and bacitracin were discontinued, and fortified tobramycin and fortified vancomycin drops were initiated. Culture results were positive for coagulase-negative *Staphylococcus* in the right eye, and *Staphylococcus hominis*, *Staphylococcus mitis*, and *Staphylococcus viridans* in the left eye. Two weeks after the appearance of keratitis, both eyes were noted to be healing. The patient was scheduled for outpatient follow-up after discharge, but outpatient care was not reestablished.

**DISCUSSION**

In the current study, 8 eyes (4 patients) that underwent treatment for ROP developed infectious ulcerative keratitis. Immediately after each surgical procedure, each affected eye was documented to have no sign of keratitis. However, each of the 8 eyes eventually developed bilateral infectious ulcerative keratitis, which was preceded by a corneal epithelial defect and corneal haze.

Infectious ulcerative keratitis should be considered as a potential but infrequent complication of ROP treatment, including indirect laser photocoagulation and PPV. In our study, 4.08% of eyes undergoing laser photocoagulation ultimately developed infectious ulcerative keratitis, whereas 33.33% of eyes that underwent PPV developed infectious ulcerative keratitis. It should be noted that the numbers in each group were extremely low (12 in laser treatment and 4 in PPV). Ocular manipulation during PPV may have caused micro-corneal abrasions, increasing the risk of infectious ulcerative keratitis.

Each eye, irrespective of being in the laser or PPV group, that developed infectious ulcerative keratitis first developed an epithelial defect followed by corneal haze. In premature infants, epithelial defects with corneal haze may be an early sign of infectious ulcerative keratitis. With the average time between epithelial defect and haze to keratitis both being approximately 3 days, close monitoring and expedited treatment of the epithelial defect is critical because a prolonged epithelial defect may facilitate bacterial growth.

Animal models have shown that corneal epithelial cells, especially those found in the limbus, retain stem cell properties. It is plausible that in these premature infants, the immature cornea has not achieved its full regenerative potential, and epithelial defects do not heal as quickly as in adults and have a greater risk to become infected, especially in a neonatal intensive care setting. This difference in corneal healing in adult versus young cornea has also been shown in animal models. The slowly healing epithelial defect can be a risk factor for infection. Even partial-thickness defects in the epithelium have been shown to increase adherence by bacteria, thus allowing for colonization and subsequent keratitis.

Anterior segment ischemia is a rare complication of laser photocoagulation, which is associated with cataract, iris atrophy, posterior synechiae, pigmented anterior lens capsule, and corneal edema. None of these cases had anterior segment ischemia. The corneal haze was limited focally to the epithelial defect. The other signs of anterior segment ischemia (ie, posterior synechiae, uveitis, cataract, and hypopyon) were absent.

Corneal haze developed in all eyes with epithelial defects before infectious ulcerative keratitis was diagnosed. Prior work has shown that after surface ablation laser surgery, wounded surface ablation adult cornea forms haze in 4 to 7 days. Haze in the wounded cornea has been postulated to form when underlying cells migrate toward the ocular surface and differentiate into a light-reflecting phenotype. Animal models have shown that in the wounded cornea, corneal haze typically forms in two regions: in a circumferential ring around the wound margin, and in spots within the corneal wound. This haze begins shortly after reepithelialization of the epithelial defect, and intensifies as the epithelial cells proliferate.

Culture-positive ulcerative keratitis was present in 5 (62.5%) of 8 cases, higher than what is reported.
in the literature for adults. The usual organisms found in pediatric populations are similar to those in the adult population and include coagulase-negative staphylococci, *Staphylococcus aureus*, *Staphylococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* (including *Klebsiella*, *Enterobacter*, *Serratia*, and *Proteus*). In cases of nonhealing infectious ulcerative keratitis, autograft transplant using the cleared cornea can be considered, and has proven to be successful, at the 3-year follow up. Corneal autologous grafts are preferable to allografts, but autologous grafts can be difficult in cases of extensive bilateral keratitis, because clear donor cornea is required.

In the two patients who underwent laser photoagulation and in the one who underwent PPV, the epithelial defect was not noted until several days after the procedure. Therefore, the procedure was less likely the source of the epithelial defect. One patient had bilateral epithelial defects diagnosed on the first postoperative day after PPV, which may have been caused during surgery. Direct corneal contact while administering drops, improperly placing an eyelid speculum, or drying of the corneal epithelium while the speculum is in place can result in epithelial defect formation. Improper positioning of the nasal cannula and the oxygen mask can blow air into the eye, leading to a dry cornea and an epithelial defect. Because all patients in this series had bilateral infectious ulcerative keratitis, cross-contamination cannot be ruled out; separate drops should be used in each of the eyes.

It is unknown if the corneas of premature infants are more susceptible to developing infectious ulcerative keratitis. Rates of premature infant births are increasing, and it is important to avoid situations that may lead to epithelial defects and increase the risk of infectious keratitis.

**REFERENCES**