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Incidence of cataract development by 6 months' corrected age in the Early Treatment for Retinopathy of Prematurity study

Bradley V. Davitt, MD[a], **Stephen P. Christiansen, MD**[b], **Robert J. Hardy, PhD**[c], **Betty Tung, MS**[c], and **William V. Good, MD**[d] **on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Groups**[*]

[a]Departments of Ophthalmology and Pediatrics, Cardinal Glennon Children's Medical Center, Saint Louis University School of Medicine, St. Louis, Missouri

[b]Departments of Ophthalmology and Pediatrics, Boston University School of Medicine, Boston, Massachusetts

[c]University of Texas Health Science Center at Houston, School of Public Health, Houston, Texas

[d]Smith-Kettlewell Eye Research Institute, San Francisco, California

Abstract

Purpose—To report the incidence of cataract development by 6 months' corrected age in preterm children who participated in the Early Treatment for Retinopathy of Prematurity (ETROP) study.

Methods—Infants who developed prethreshold ROP in one or both eyes and were determined by the RM-ROP2 model to have a high risk of poor structural outcome without treatment were randomized to receive early treatment (ET), defined as laser photocoagulation at high-risk prethreshold ROP, or to be conventionally managed (CM), receiving treatment only if threshold ROP developed. Data on eyes developing a cataract by 6 months' corrected age was analyzed.

Results—Of 401 randomized infants, 366 survived patients were followed, and 8 eyes of 7 patients (1.9%) developed cataracts by 6 months' corrected age. Among these patients, mean birth weight was 754 g, and mean gestational age was 25.7 weeks. Mean gestational age at treatment was 36.3 weeks for ET patients and 39.5 weeks for CM patients. Three ET eyes and 5 CM eyes developed a cataract. Of the CM eyes, 3 with and 2 without laser treatment developed a cataract. All 6 treated eyes had plus disease when treated. Three eyes had ROP in zone 1, whereas the other 3 had ROP in zone 2. All eyes were treated using a diode laser.

Conclusions—By 6 months' corrected age, a small number of both ET and CM eyes developed cataracts following diode laser treatment for retinopathy of prematurity. Absence of obvious intraoperative complications does not preclude subsequent cataract development, which can occur without laser treatment.

Correspondence: Bradley V. Davitt, MD, Cardinal Glennon Children's Medical Center, 1465 South Grand Boulevard, Saint Louis, MO 63104 (davittb@slu.edu).

[*]A list of the members of the Early Treatment for Retinopathy of Prematurity Cooperative Group is provided as e-Supplement 1, available at jaapos.org.

Whereas cataracts have been a well-recognized complication of stage 4 or 5 retinopathy of prematurity (ROP), the incidence of cataract development following treatment at earlier stages has not been firmly established.[1,2] Cataracts were not observed as a complication of treatment in the CRYO-ROP study.[3-5] As cryotherapy for ROP became the standard of care, numerous immediate ocular complications were documented, but cataract development was not among them.[6] By the early 1990s, cryotherapy was mostly replaced by transpupillary laser photocoagulation, which was considered safer and less stressful to the infant. However, a large randomized study comparing the safety and efficacy of laser treatment to cryotherapy was never performed, and the true incidence of cataract development following laser treatment is unknown. The purpose of this study is to report the incidence of cataract development in patients up to 6 months' corrected age following randomized treatment in the ETROP trial.

Subjects and Methods

Infants with birth weights ≤1,250 g born between October 1, 2000, and September 30, 2002, were screened at 26 participating centers. The ETROP study protocol was reviewed and approved by the institutional review boards of all centers in accordance with the US Health Insurance Portability and Accountability Act. The parents or legal guardians of infants who developed high-risk prethreshold ROP as determined by the RM-ROP2 model[7] provided consent for the randomized trial. If both of the patient's eyes were high risk, one eye was randomized to early treatment (ET), and the other eye was managed conventionally (CM) and treated if it reached threshold by standards established by the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Cooperative Group.[3] If only one eye was at high risk, it was randomly assigned to early treatment or conventional management. The details of the randomization process have been published elsewhere.[8,9] Patients receiving treatment were examined within 10 days of surgery. Structural outcome, including a dilated fundus examination, was documented at 6 months' corrected age by study-certified examiners. For eyes that developed a cataract, ROP characteristics, operative details, and ocular complications at the time of laser treatment as well as any complications occurring within 10 days of surgery were documented.

Results

Of 401 infants randomized into the study, 366 survived patients were followed. Of these, 290 subjects had 2 study eyes, yielding a total of 656 study eyes. Of these, 330 were assigned to the ET group, and 326 were assigned to the CM group, two-thirds of whom received treatment at threshold. In 7 patients (4 males), 8 eyes (1.9%) developed a cataract by 6 months' corrected age. With the exception of one African American patient who was conventionally managed and did not receive treatment, all other patients were white. For patients who developed a cataract, the mean birth weight was 754 g (range, 614-1020 g), and the mean gestational age was 25 weeks, 5 days (range, 23-27 weeks). Three ET eyes and 5 CM eyes developed a cataract. Of the CM eyes, 3 that received laser treatment and 2 without laser treatment developed a cataract. The mean gestational age at the time of treatment for ET patients who developed a cataract was 36.3 weeks, whereas that for CM patients was 39.5 weeks. Of the 6 eyes that developed cataracts following laser treatment (both ET and CM), 3 had ROP in zone 1 and the other 3 had ROP in zone 2 at the time of treatment. All eyes were documented to have plus disease at the time of treatment. Four eyes developing a cataract after laser treatment had persistent pupillary vessels at the time of treatment, and the other 2 did not. In a patient who developed bilateral cataracts, persistent pupillary vessels were noted at the time of laser treatment in the CM eye receiving treatment, but they were not present in the ET eye. A diode laser was used in each eye receiving treatment. A 20 D condensing lens was used in 3 treated eyes that developed a

cataract; a 30 D lens was used in 2 treated eyes; a 28 D lens was used in the remaining treated eye. The total number of laser applications for each eye is listed in Table 1. No complications at the time of treatment, including conjunctival or subconjunctival hematoma, conjunctival laceration, hyphema, hemorrhage (retinal, preretinal, or vitreous), central retinal artery occlusion, or inadvertent burn or freeze to an area outside of the target zone was reported in any treated eye which developed a cataract. By 10 days postoperatively, 3 eyes were reported to have complications. One eye developed a hyphema; another eye developed a retinal, preretinal, or vitreous hemorrhage. Only 1 treated eye was reported as having developed a cataract within 10 days of treatment. The type of cataracts that developed and associated ocular findings are reported in Table 1.

Discussion

The incidence of cataract development following ROP treatment is not well established and may be underreported. Recognizing this, in 1995 Gold[10] surveyed members of the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) regarding their method of ROP treatment and whether cataracts had occurred in their individual series. A total of 34 visually significant cataracts were reported as complications of ROP treatment, 22 associated with argon laser therapy and 9 with diode laser; cryotherapy was associated with 3 visually significant cataracts. Of ophthalmologists surveyed, 71% were treating ROP with laser rather than cryotherapy, and nearly twice as many respondents used diode laser than argon laser therapy. A similar survey of ROP treatment in the United Kingdom was performed in 2004. No cataracts were reported using diode or argon laser, while 2 cataracts were reported using the FD-YAG laser. Of 30 respondents treating ROP, 19 used diode laser, 11 used argon laser, and 3 used FD-YAG laser.[11]

Since cataract formation poses a significant threat to visual development in an infant, knowledge of its incidence may play an important role in framing the discussion of risks and benefits of ROP treatment. Since laser photocoagulation became the favored treatment for ROP, several small studies have reported no significant cataract formation.[12-15] Other case reports suggested a risk of cataract formation with laser photocoagulation in the treatment of ROP. Drack and colleagues[16] were the first to describe transient punctate lenticular opacities as a complication of argon laser photocoagulation in an infant with ROP, suggesting that the lens changes seen were a result of heat transferred from laser energy absorbed by vessels on the lens capsule. Pogrebniak and colleagues[17] reported a dense, mature cataract after an infant with ROP was treated with an argon laser and proposed that treatment had ruptured the lens capsule.

Christiansen and Bradford[18] reviewed 100 consecutive eyes receiving argon laser photocoagulation for threshold ROP and found that 6 eyes (6%) developed complete lens opacification. The eyes were noted to have prominent tunica vessels at the time of treatment. No lens opacities or iris or corneal burns were noted in any eye either during laser application or immediately postoperatively. After treatment, the eyes developed hyphema, shallowing of the anterior chamber, corneal edema, and progressive lens opacification. Additionally, posterior synechiae, iris stromal atrophy, and pigment epithelial atrophy were noted in each affected eye, usually at the time the cataract was diagnosed. No statistically significant relation was found between development of cataract and the number of burns, zone, or clock hours of extraretinal proliferation, birth weight, gestational age, or age at treatment. O'Neil and colleagues[19] reported a cataract incidence of 1% in a group of 374 eyes with threshold ROP treated with argon laser. Each of the 4 eyes that developed cataracts subsequently developed microphthalmos. While persistent tunica vessels were noted in 41% of infants, they were seen in all patients in whom a cataract developed.

The diode laser, which emits radiation at 810 nm and has minimal absorption by hemoglobin, has been suggested as a safer choice compared with other laser wave lengths.[18,20] However, cataracts have also been reported using the diode laser. Capone and Drack[20] reported transient clear cavitary lens changes after diode laser treatment for ROP occurring during the procedure itself. Campolattaro and Lueder[21] were the first to report a dense, mature cataract using a diode laser and suggested that it developed primarily as a result of uveal effusion, noting that uveal effusion after panretinal photocoagulation in adults is thought to result from choroidal inflammation and that thermal injury to the choroid in animals[22] has been shown to be greater with diode than with argon laser. Christiansen and Bradford[23] also reported a patient treated with diode laser that developed bilateral cataracts following treatment: B-scan ultrasonography failed to demonstrate any evidence of uveal effusion, but signs of anterior segment ischemia were noted. Paysee and colleagues[24] reported the incidence of acquired cataract after diode laser photocoagulation for threshold ROP. Of 293 eyes, 1 (0.003%) developed small, nonprogressive peripheral cortical lenticular opacities, which were noted shortly after treatment. This low incidence and the absence of visually significant cataracts in their cohort suggested an advantage of diode over argon laser, but the results are not definitive. More recently, Kieselbach and colleagues[25] reported 1 of 37 (3%) eyes treated with diode laser developing cataract requiring extraction.

In the ETROP study, 6 of the 8 eyes that developed cataracts before 6 months of age received laser treatment, all with the diode laser but using different condensing lenses and number of burn spots. Only 1 of these eyes was reported as developing a cataract within 10 days of treatment. In this particular case, no other complication during the treatment such as inadvertent burn or postoperative complication, such as hyphema or vitreous hemorrhage was reported, so the mechanism of cataract formation remains unclear. While only white infants developed cataracts following treatment, no other demographic information such as sex, birth weight, or age at treatment were identified as independent risk factors.

Several case series of cataracts following ROP treatment have contributed to our understanding of associated ocular findings supportive of an anterior segment ischemia etiology.[26-28] Simons and colleagues[26] reported a case of bilateral cataracts following diode laser treatment in eyes without obvious preexisting abnormalities (eg, persistent tunica vasculosa lentis, dilated iris vessels, or poor dilation) with associated ciliary flush, bilateral hyphemas, normal intraocular pressure, and B-scan ultrasonography revealing choroidal thickening. Lambert and colleagues[27] reported 10 eyes with cataracts, half treated with diode laser and half with argon laser. The clinical findings were most consistent with anterior segment ischemia, citing similarities noted by Freeman and colleagues in a rabbit model.[29] Nine of the 10 eyes progressed to phthisis bulbi with no light perception. Kaiser and Trese[28] reported 8 eyes developing cataract as a complication following diode laser photocoagulation (7) or cryotherapy (1) and proposed a possible mechanism for developing anterior segment ischemia: a combination of impairment of blood flow in the long posterior ciliary arteries via scleral depression and simultaneous confluent tissue ablation.

In the 6 eyes that developed cataracts following laser treatment in the ETROP study by 6 months' corrected age, there was some evidence that anterior segment ischemia may have caused cataract development. By 6 months' corrected age, 1 eye showed corneal opacification, 1 eye was found to have iris atrophy, 2 eyes had shallow anterior chambers, and 3 eyes had evidence of iris synechiae. At time of treatment, 4 of 6 eyes had persistent pupillary vessels, and all eyes had plus disease, suggesting that the presence of these findings may be associated with cataract development. The mechanism by which the presence of pupillary vessels or plus disease may be related to postoperative anterior segment ischemia is unclear.

Since publication of the ETROP study results, ophthalmologists are no longer waiting until threshold ROP develops to offer treatment. Recently Salgado and colleagues[30] suggested that infants treated with laser at a younger postmenstrual age may be more susceptible to postoperative anterior segment complications. They reported on 259 eyes of 184 patients treated with diode laser for ROP between 1995 and 2007, with 120 eyes treated at pretheshold and 139 eyes treated at threshold. Thirteen (10.8%) eyes treated at prethreshold were found to have an anterior segment complication after laser treatment compared to none of the eyes treated at threshold ROP. All 13 eyes had hyphema, and 3 of these eyes (2.5%) also had cataracts. Two eyes with dense cataracts requiring extraction were suspected of anterior segment ischemia because of the subsequent appearance of iris atrophy, hypotony, and minimal growth of the eyes. In contrast, our experience suggests that earlier treatment is not associated with an increased incidence of cataract development because of the 6 eyes developing cataracts following laser treatment, 3 had been treated early and 3 had been conventionally managed.

In a recently published report regarding the efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity, Mintz-Hittner and colleagues[31] randomly assigned patients to undergo intravitreal bevacizumab monotherapy or conventional laser therapy. Of 73 patients receiving conventional laser therapy, 3 (4.1%) developed lens opacities requiring cataract removal. Each of these patients has posterior zone 2 ROP. The type of laser used was not described. Our overall incidence of cataract development may be slightly underestimated. Despite excellent follow-up for a study of this size, cataract development in those patients who were lost to follow-up cannot be ruled out. Additionally, the ETROP study was not designed to determine the incidence of cataract development, and subjects in this study represent a select group of high-risk patients not representative of the general population.

While our findings suggest that cataract development must be considered a very real and potentially devastating visual complication followinglaser photocoagulation for treatment of ROP, 2 of our patients developed cataracts without treatment. This suggests that cataract development following laser treatment of ROP cannot always be attributed to the treatment. Lastly, even in the absence of complications at time of laser treatment or lack of immediate postoperative cataract changes, the risk of cataract development remains, and close follow-up is warranted to at least 6-month corrected age and likely beyond.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Eyes developing a cataract in the ETROP study by 6 months' corrected age

EYE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
AT TREATMENT					Same patient			
ET/CM (if CM, CM (treated-T or not- no))	CM(T)	ET	CM(no)	CM(no)	CM(T)	ET	CM(T)	ET
Age at treatment, weeks	41.1	38.4			39.4	34.9	38.1	35.7
Zone at treatment	1	2			1	1	2	2
Plus at treatment	Y	Y			Y	Y	Y	Y
Persistent pupillary vessels	Y	Y			Y	N	Y	N
Laser used	Diode	Diode			Diode	Diode	Diode	Diode
Lens used	20	28			30	30	20	20
Total number laser applications (CYRO), if / means retreatment	3249(5)	3945			2206	1115/297	1781/439	677
OCULAR COMPLICATIONS AFTER TREATMENT (WITHIN 10 DAYS)								
Postoperative external infection?	N	N			N	N	N	N
Conjunctival or subconjunctival hematoma	N	N			N	N	N	N
Hyphema	Y	N			N	N	N	N
Ocular motility disturbance	N	N			N	N	N	N
Proptosis	N	N			N	N	N	N
Enophthalmos or narrowed lid fissure other than from edema	N	N			N	N	N	N
Perforation of globe	N	N			N	N	N	N
Cataract	UG[a]	N			N	N	Y	N
Hemorrhage: retinal, preretinal, vitreous	UG	N			Y	N	N	N
Inadvertent burn or freeze to area outside of target zone	UG	N			N	N	N	N
Persistent closure of central retinal artery	UG	N			N	N	N	N
Exudative retinal detachment	UG	N			N	N	N	N
AT 6 MONTHS' CORRECTED AGE EXAM								
Corneal opacification	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Present
Depth of anterior chamber	Shallow	Shallow	Normal	Normal	Normal	Normal	Normal	Normal
Synechiae	Present	Absent	Absent	Absent	Present	Present	UG	Present
Iris atrophy	Present	Absent	Absent	Absent	Absent	Absent	UG	Absent

EYE	1	2	3	4	5	6	7	8
Cataract type[b]	1	1,2,3	4	4	5	5	1	2

CM, conventional managed eyes; *CM(no)*, CM untreated; *CM(t)*, CM treated; *ET*, early treated eyes; *UG*, unable to grade.

[a]1 = visually significant; 2 = cortical, 3 = posterior subcapsular; 4 = focal, not on visual axis; 5 = other.