Diode Laser Photocoagulation for Threshold Retinopathy of Prematurity

A Randomized Study

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Background: Although peripheral cryotherapy decreases the incidence of unfavorable anatomic outcomes in threshold retinopathy of prematurity (ROP), apnea, bradycardia, and lid edema can occur. Argon laser indirect ophthalmoscope photocoagulation has been used as an alternative to cryotherapy, with fewer adverse effects. Retinal lesions placed with diode lasers are deeper than similar argon laser lesions, and it is not known whether this difference could influence the response to ablative therapy.

Methods: Patients were enrolled under a prospective, randomized protocol. One eye of each patient with symmetric, threshold ROP was treated with an 814/815 nm diode laser, while the other eye was treated with cryotherapy. Patients with asymmetric disease also were randomized for treatment in the threshold eye.

Results: Nineteen infants (33 eyes) were treated, ranging from 485 to 863 g birth weight (23 to 27 weeks gestational age); 18 patients (32 eyes) were followed for 3 months or longer. Four patients (8 eyes) had bilateral zone 1 disease. Postconceptional age was 36 to 45 weeks at the time of treatment. The diode laser treatment was better tolerated than cryotherapy, and the treatment apparatus was more easily transported. Apneic episodes requiring intubation resulted from two cryotherapy sessions but no diode laser sessions. Five cryotherapy-treated eyes required retreatment because of persistent disease with adjacent skip areas. In the group followed for 3 to 15 months, 1 cryotherapy-treated eye and 1 diode laser-treated eye progressed to stage 5 retinal detachment.

Conclusion: Compared with cryotherapy, the diode laser was more convenient, technically easier to administer, and better tolerated by the patient. Although the number of patients was too small for meaningful statistical analysis of outcome, diode laser peripheral retinal ablation appeared to be as effective as cryotherapy for the treatment of threshold ROP. *Ophthalmology 1993;100:238–244*

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Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retinal vasculature of preterm infants.[1] With advances in neonatology and the improved survival of extremely low birth weight infants,[2] the incidence of ROP has been increasing over the past two decades.[3] Cryoablation of the avascular peripheral retina arrests the progression of threshold ROP in a significant percentage of patients.[4] However, cryotherapy damages the sclera of the developing newborn eye, the treatments are painful and associated with frequent systemic complications, and the equipment is cumbersome to use. McNamara et al[5] and Iverson et al[6] have compared argon laser indirect ophthalmoscope peripheral retinal ablation with cryotherapy in controlled studies and found equal

efficacy with fewer systemic complications. Landers et al[7] also treated threshold disease successfully with the argon laser in an uncontrolled study. Still, the argon laser is fragile and bulky, making it difficult to transport. Furthermore, argon laser energy can be absorbed by structures in the anterior segment, resulting in corneal epithelial edema,[7] burns of the cornea and iris,[8] and coagulation of the tunica vasculosa lentis with secondary miosis.[9]

The GaAlAs diode laser is a solid state device that has been adapted for use with an indirect ophthalmoscope. The diode laser equipment is sturdy and portable—two distinct advantages in a neonatal intensive care unit. It operates on ordinary current, requires no special cooling, and can be carried in a briefcase. The diode laser uses near-infrared energy for retinal ablation, which is minimally absorbed by the cornea and tunica vasculosa lentis. Diode laser energy is delivered deeper in the retina than argon laser energy, and it is not known whether this difference in wavelength would influence the response to therapy. To date, there has been no published report of an attempt to compare cryotherapy with diode laser for treatment of threshold ROP. In this study, patients with threshold ROP were randomized to cryotherapy or diode laser ablation of the peripheral avascular retina to compare these treatment methods.

Patients and Methods

Screening and Randomization

All preterm infants at the Johns Hopkins Hospital and affiliated hospitals (Francis Scott Key Medical Center, Union Memorial Hospital, and Greater Baltimore Medical Center) weighing less than 1500 g at birth, and larger infants treated with supplemental oxygen for more than 50 days, were screened. All patients received surfactant prophylaxis per hospital protocol at the time of delivery. Infants were examined 5 to 6 weeks after delivery and at subsequent biweekly intervals. Two drops of cyclopentolate 0.2%/phenylephrine 1.0% (Cyclomydril) were instilled 5 minutes apart 1 hour before examination by indirect ophthalmoscopy with scleral depression. Examinations were recorded on a standardized data sheet. When prethreshold (any disease in zone 1, or plus disease with less than 5 contiguous or 8 interrupted clock hours in zone 2) was reached, weekly examinations were performed. The presence of threshold disease, as defined by the CRYO-ROP protocol, always was confirmed by the same examiner (MXR) before treatment.

When one or both eyes reached threshold, informed consent was obtained from the parents to enter their child into an institutionally approved Johns Hopkins Clinical Investigation Protocol. In patients with symmetric disease, the eye to be treated first and the treatment method were randomized. Treatment of the first eye was initiated within 48 hours of recognition of threshold disease. The second eye was treated by the other technique within 48 hours of treatment of the first eye, and both eyes were treated within 72 hours. Logistic considerations mandated that both eyes be treated in the same session (by different techniques) in some cases. In patients with asymmetric disease, the treatment technique was chosen by a randomized envelope drawing. If the other eye subsequently progressed to threshold, it was treated by the other method.

Premedication and Treatment

Treatments were performed in the neonatal intensive care unit with continuous monitoring of heart rate, respiratory rate, and oxygen saturation. Two sets of dilating drops (as described above) were instilled 1 hour before treatment. Oxygen (0.2 to 0.5 l/minute) was administered by nasal cannula. Intravenous premedication of atropine 0.01 mg/kg, followed by morphine 0.1 mg/kg, was administered. Proparacaine 0.5% was instilled, and an Abraham lid speculum was placed in the eye. In some cases, analgesia or anesthesia was supplemented with additional doses. The extent and severity of disease were assessed and photographed with a Kowa RC-2 camera (Kowa Optimed, Inc., Torrance, CA) whenever possible.

Cryotherapy was administered using a Frigitronics cryotherapy unit (Frigitronics, Inc., Shelton, CT) equipped with a 1-mm pediatric cryotherapy probe. Contiguous cryotherapy applications of moderate intensity were used to obliterate the avascular retina. Lesions were placed from immediately anterior to the ridge to the ora serrata over 360°. In some cases, topical glycerin 50% ophthalmic solution was used intraoperatively to minimize corneal haze.

A dual semiconductor IRIS OcuLight SLx (IRIS Medical Instruments, Mountain View, CA), 813/814-nm, 2° convergent cone angle, GaAlAs diode laser indirect ophthalmoscope with a 200-μm fiberoptic delivery system was used for photoablation. Lesions were delivered through a Nikon 28 diopter aspheric indirect ophthalmoscopy lens, for a spot size of approximately 600 μm. An initial intensity of 320 mW with a 300-msec duration was increased as needed until an unequivocal creamy white lesion of the pigment epithelium was observed with each application. The entire avascular retina was treated with noncontiguous applications separated by 150 to 300 μm. A Flynn lens loop was used for scleral depression to visualize and treat the peripheral retina. The lens loop provided satisfactory stabilization of the globe during the treatment sessions. Immediately after treatment, the eye was examined with a hand magnifier for evidence of injury to the anterior segment, conjunctiva, or lids.

Postoperatively, patients were monitored in the intensive care unit for a minimum of 16 hours. Homatropine 2% and prednisolone 0.6%/gentamicin 0.3% (Pred-G) were administered for 3 to 5 days. Follow-up examinations were performed weekly until regression and every 3 months subsequently, with more frequent examinations as indicated by the severity of disease. If plus disease was unchanged or worse at 10 to 14 days in eyes with persistent extraretinal fibrovascular proliferation adjacent to untreated ("skip") areas, the skip areas were retreated. During follow-up examinations, patients were assessed for the presence of vitreous hemorrhage, plus disease, iatrogenic complications such as lid swelling, chemosis, anterior seg-

Table 1. Characteristics of Patient Population

Patient No.	Gestational Age (wks)	Birth Weight (g)	Sex	Race	Eye(s) Treated	Follow-up (mos)
1	24	583	F	W	1 (diode)	12
2	26	670	F	W	2	11
3	26	485	M	B	2	4
4	25	863	M	W	1 (diode)	15
5	25	676	M	B	2	11
6	27	836	F	W	2	12
7	23	730	F	W	2	6
8	24	690	M	B	2	14
9	24	595	F	W	1 (diode)	9
10	24	634	F	B	1 (cryo)	3
11	25	650	M	B	2	3
12	24	570	M	B	2	6
13	25	804	M	W	2	7
14	25	567	M	B	2	5
15	25	665	M	W	1 (diode)	1*
16†	25	670	M	B	2	4*
17†	25	625	M	B	2	4
18	25	610	M	W	2	4
19	26	540	M	W	2	4
Mean	24.8	656	68% M	47% B	—	7

* Patient died.

† Twins.

ment photocoagulation scars, or macular injury, and for sequelae of ROP including straightening of vessels, macular ectopia, and myopia.

Unfavorable anatomic outcomes were defined as specified by the CRYO-ROP study. These included posterior retinal folds through the macula, retrolental opacities, pupillary occlusion, and posterior retinal detachment.

Results

Patient Population

The parents or guardians of all 19 eligible infants from four nurseries agreed to participate in the study. Gestational age ranged from 23 to 27 weeks, with birth weights of 485 to 863 g (Table 1). Fourteen patients had symmetric disease. Four infants (patients 6, 14, 16, and 17) had bilateral anterior zone 1 disease; the remainder of eyes had disease in zone 2.

Treatment and Treatment Complications

The cryotherapy and diode laser-treated groups are compared in Table 2. Age at treatment ranged from 10 to 16 weeks (36 to 41 weeks postconceptional age). Both treatment groups had an average of 9 clock hours of disease. Treatment intensity for laser-treated eyes ranged from 330 to 520 mW, with the number of applications ranging from 220 to 923 depending on disease location. In the cryotherapy-treated eyes, 20 to 68 applications were required for complete coverage of the avascular retina. Conjunctival incisions were not required for any treatment session.

Table 2. Comparison of Mean Values in Cryotherapy and Diode Laser Groups

Method	Gestational Age (wks)	Birth Weight (g)	Age at Diagnosis (wks)	Postconceptional Age at Diagnosis (wks)	Extent (clock hrs)	Sex (% Male)	Race (% Black)
Cryo	25	650	12	37	9	73	60
Diode	25	657	13	38	9	72	44

The diode laser and cryotherapy sessions lasted between 15 and 45 minutes. It was technically easier to place the lesions using gentle scleral depression and the aiming beam of the diode laser compared with the pressure, manipulation, and globe distortion required for accurate placement of the cryotherapy probe. This was most notable in patients with posterior disease, where extreme cryotherapy probe manipulations were required to reach areas that might have required no scleral depression had the diode laser been used. While a cryotherapy lesion covered a larger retinal area than a diode laser lesion, 5 to 10 diode laser applications could be delivered in the same amount of time as a single cryotherapy lesion.

In patients with hazy media at the time of treatment with the diode laser, the red aiming beam remained visible on the retina, which facilitated accurate placement of lesions. In contrast, the tip of the cryotherapy probe was occasionally difficult to visualize until after the pedal had been depressed and the yellow cryo lesion became visible. The diode laser energy passed through vitreous blood, making it possible to photocoagulate the retina behind areas of vitreous hemorrhage. The presence of a persistent tunica vasculosa lentis did not interfere with diode laser or cryotherapy treatments, with no evidence of energy absorption by lens vessels and no intraoperative miosis.

During one diode laser and one cryotherapy session, the patient began crying during treatment. In both cases, supplemental morphine was administered and the treatment resumed without difficulty. Patient discomfort as indicated by heart rate, respiratory rate, and patient activity did not appear to differ between the cryotherapy and diode laser groups, although these parameters (maximum and minimum heart rate and respiratory rate during treatment) were not quantitated in all cases.

Treatment complications were seen more frequently in cryotherapy-treated eyes (Table 3). All cryotherapy-treated eyes had more conjunctival and periorbital edema after treatment than diode laser-treated eyes (Fig 1). One inadvertent conjunctival laceration occurred during a cryotherapy session in a patient with zone 1 disease. In one diode laser-treated patient, a 600-μm subretinal hemorrhage indicative of Bruch's membrane rupture occurred. No corneal, iris, or lens burns were observed. No diode laser treatments were interrupted by sustained systemic reactions and none resulted in intubation.

Table 3. Treatment Complications of Cryotherapy Versus Diode Laser Photocoagulation for ROP

Complication	Cryotherapy (n = 15)	Diode Laser (n = 18)
Transient corneal clouding	2	0
Retreatment	5*	0
Interrupted session (apnea or bradycardia)	2	0
Intubation (intra- or postoperative)	2	0
Conjunctival laceration	1	0
Bruch's membrane rupture	0	1

Numbers indicate number of treatment sessions associated with the indicated complication.

* $P = 0.013$, Fisher exact test.

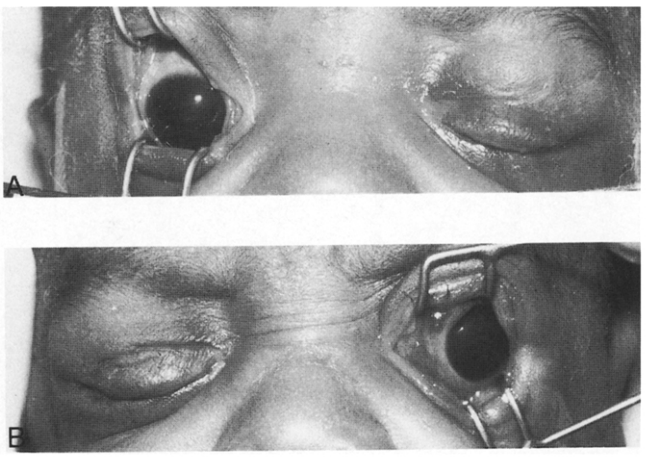

Figure 1. Ocular swelling after treatment (patient 11). **A,** immediately after treatment with the diode laser in the right eye. The left eye had been treated 48 hours earlier by cryotherapy but still demonstrates more periocular swelling. **B,** immediately after treatment with cryotherapy in the left eye. There is marked conjunctival swelling compared with the diode laser-treated eye.

Postoperative Course

Time of follow-up ranged from 1 to 15 months, with a mean of 7 months (Table 1). Five cryotherapy-treated eyes required retreatment for persistent disease (Table 3) ($P = 0.013$ by Fisher exact test). Eighteen (32 eyes) were followed for 3 months or longer. Small vitreous hemorrhages occurred in two cryotherapy and three diode laser-treated eyes.

One patient with 12 clock hours of disease before treatment (patient 3) had questionable dragging of vessels and macula temporally (less than 1 disc diameter, as defined in the CRYO-ROP Phase II Manual of Procedures, Portland, OR, 1992) in both the diode laser and cryotherapy-treated eye. One cryotherapy-treated eye with zone 1 disease (patient 14) and one diode laser-treated eye with zone 1 disease (patient 16) progressed to stage 5 retinal detachment. Before treatment of each of these eyes, a large preretinal hemorrhage (>7 mm) was present.

After 1 month, cryotherapy-treated eyes had extensive chorioretinal atrophy in the treated areas. The diode laser-treated eyes (Figs 2 and 3) had less extensive scarring, with areas of vascularized retinal tissue remaining between the photocoagulation scars.

Discussion

Attempts to reattach the retinas in eyes with advanced ROP have met with mixed anatomic success and disappointing functional results[10,11]; thus, the emphasis for

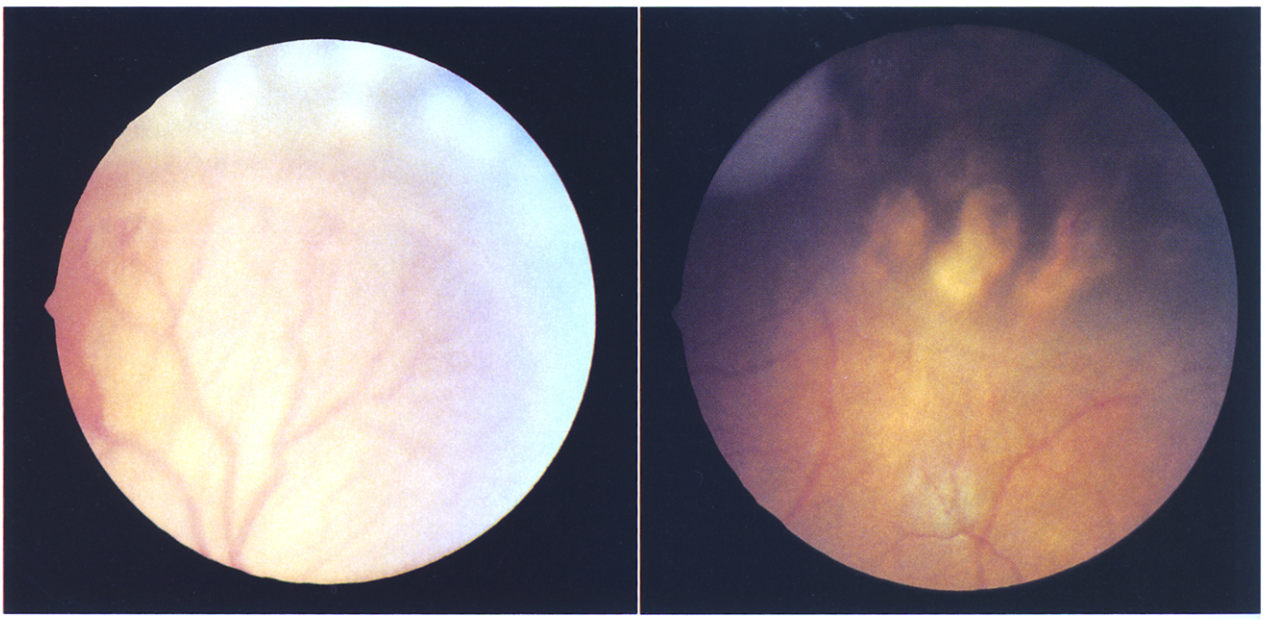

Figure 2. Threshold ROP immediately after treatment with the diode laser (patient 5). The diode laser lesions, which were placed ¼ to ½ spot-width apart, have a creamy white appearance.

Figure 3. Same eye of patient 5, 1 month after treatment. The laser lesions have matured with minimal spreading, leaving isthmuses of intact peripheral retina, choroid, and sclera.

prevention of blindness from ROP has been on recognizing potentially severe disease and preventing retinal detachment. Cryotherapy in acute retinopathy of prematurity induces regression, either by destruction of angiogenic factors in the peripheral retina or possibly by induction of anti-angiogenic factors. The clinical efficacy of cryoablation of peripheral retina in inducing regression of severe ROP has been documented in the CRYO-ROP multicenter clinical trial.[4]

Photocoagulation of the peripheral retina was the first proposed method of treatment for ROP,[12,13] however the lasers available at that time made such therapy extremely demanding technically. With the advent of indirect ophthalmoscope-mounted argon blue–green lasers, interest in treating threshold ROP with this technique has surged. The argon laser damages all layers of the retina equally from inner plexiform layer to pigment epithelium,[14] with less effect on the choriocapillaris and no damage to sclera. The semiconductor diode laser emits coherent light in the near-infrared range, which results in distinctive absorption behavior[15] and histologically different photocoagulation scars.[16] At lower power levels, the long wavelength light passes through the inner layers of retina without inflicting significant direct damage until it reaches the pigment epithelium and choriocapillaris.[17] While this may be an advantage in the treatment of subretinal neovascular disease in adults, it is a potential disadvantage in ROP. Kretzer et al[18] have proposed that spindle cells are capillary endothelial precursors in the immature retina that contribute to the course of ROP. These cells, which are present in large numbers in the inner retinal layers, might be spared injury by lighter treatment with the diode laser, allowing the disease stimulus to remain.

Therefore, to maximize the potential effectiveness of treatment, lesion intensity was adjusted in an attempt to extend damage into the inner layers of the retina to assure destruction of all retinal layers. The creamy white lesions used in this study appeared similar to those that damaged all layers of retina in the rabbit[17] and monkey.[19] This lesion intensity caused a clinically evident subretinal hemorrhage suggestive of rupture of Bruch's membrane in only one case.

Although the benefits of argon laser therapy have been documented less extensively than those of cryotherapy, results to date suggest that argon laser treatment is as effective as cryotherapy in decreasing the incidence of unfavorable anatomic outcomes. McNamara et al[5] performed a randomized trial of 22 patients with threshold ROP and found regression of ROP in 15 of 16 laser-treated eyes and 9 of 12 cryotherapy-treated eyes, with 3 months of follow-up. Iverson et al[6] obtained similar results in a smaller group (12 eyes). Landers et al[7] treated 9 patients with an argon blue–green laser in an uncontrolled study, with 4 eyes (27%) progressing to unfavorable outcomes with 6 to 12 months of follow-up.

There are drawbacks to treatment with the argon laser. It is relatively inefficient, resulting in a large, water-cooled instrument with high power consumption. Absorption of blue–green laser energy by other ocular structures can lead to complications. Four argon laser sessions of Landers et al[7] were interrupted by corneal haze requiring epithelial debridement, possibly due to corneal absorption. Five eyes developed pupillary constriction during treatment, and

iris photocoagulation burns were observed in five eyes as well.[7] Coagulation of the tunica vasculosa lentis and absorption of the blue–green light by vitreous opacities or preretinal hemorrhage also can make treatment difficult and limit the amount of photocoagulation that can be performed.

Although the rate of unfavorable anatomic outcomes in this study (6%) was much lower than that observed in treated eyes of the CRYO-ROP study[4] (25.7%), it is unlikely that birth weight contributed to this difference. Compared with the CRYO-ROP study, the patients in this study had a lower birth weight (656 versus 800 g) and gestational age (24.8 versus 26.3 weeks), which would put the patients at a higher risk for an unfavorable outcome. The birth weight and gestational age of patients treated by McNamara et al[5] (785 g, 26.5 weeks) and Landers et al[7] (808 g, 26.2 weeks) also were higher than in the current study. The lower birth weight in our patient population may have been a consequence of surfactant prophylaxis, which in our experience reduces the severity of ROP in larger infants and improves survival of smaller infants.[2] The presence of vitreous hemorrhage preoperatively in both eyes that progressed beyond stage 3 indicates that this may be a poor prognostic factor, perhaps due to formation of a focus for fibrovascular proliferation.

Although the patient population was too small for meaningful statistical analysis of outcome, the diode laser appeared to be as effective as cryotherapy in inducing regression of acute threshold ROP. Compared with cryotherapy, treatment was well tolerated with no serious systemic reactions and no retreatments for persistent disease. In contrast with the argon laser, there was no difficulty treating through hazy media and no apparent damage to the anterior segment. Treatment of eyes with hazy media was in fact easier with the diode laser than with cryotherapy. Treatment of posterior disease, especially zone 1 disease, also was considerably easier technically. Overall damage to the periphery of the fundus was much less extensive in the diode laser-treated eyes. Iris clipping, which has been observed with other types of diode laser,[20] did not occur because of the small convergence angle of the Iris OcuLight laser.

Compared with cryotherapy, diode laser sessions are hardly more stressful than a prolonged examination, with fewer intraoperative systemic complications and less postoperative swelling of lids and conjunctiva. Treatment can be performed with topical anesthesia and intravenous sedation only. The minimal side effects and portability may avoid delays in treatment by allowing: (1) treatment of less medically stable infants who might not tolerate a session of cryotherapy, (2) treatment of both eyes of more stable infants in a single session, and (3) treatment of infants at scattered regional facilities without the need for transfer.

A statistically meaningful comparison of the efficacy of cryotherapy, argon laser, and diode laser would likely require a multicenter study.[21] However, Tasman[22] has questioned the value of such a multicenter comparison, since treatment with laser is so well tolerated compared with cryotherapy, and laser photocoagulation has been as effective as cryotherapy in all preliminary studies to date. The long-term complications of these treatments, however, remain unknown and require continued investigation as larger numbers of infants are treated. Still, given the poor prognosis of patients with threshold disease in zone 1 and of patients who progress to retinal detachment, we agree with Tasman's[22] suggestion that the power of a multicenter trial involving ROP patients might best be directed toward defining the optimal threshold[23] for treatment.

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