Combined treatment with laser photocoagulation and cryotherapy for threshold retinopathy of prematurity

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PURPOSE. *To report the structural, functional, and refractive outcome, safety, and effectiveness of combined cryotherapy and diode laser indirect photocoagulation in the treatment of threshold retinopathy of prematurity (ROP).*

METHODS. *Medical records of patients developing threshold ROP between 1995 and 2003 were reviewed to identify those with combined treatment and followed up for at least 4 years postoperatively. A total of 94 patients (172 eyes) received combined treatment. Data consisted of grade of ROP pre- and postoperatively, most recent fundus examination, birthweight, visual acuity, complications, and refraction. Diode laser was used to ablate posterior avascular retina, and cryotherapy was used for anterior retina.*

RESULTS. *A total of 149 (87%) eyes responded to combined treatment and they had favorable anatomic outcome at last examination. In 131 eyes (76%), functional outcome was favorable (visual acuity better than 20/200) at last examination. Perioperative complications included hemorrhages in 26% of eyes, which resorbed spontaneously. Mean duration of treatment was 31 minutes/eye. At final visit (4 to 12 years), 115 eyes (66.8%) refracted were myopic, of which 26 (22.5%) had high myopia over –6 diopters.*

CONCLUSIONS. *Combined cryotherapy and diode laser photocoagulation for ROP in our patients resulted in regression of threshold ROP with relatively successful structural and functional outcomes. Combined therapy may be faster and useful for eyes with very posterior ROP. This may decrease the number of complications occurring when excessive cryotherapy or laser photoablation must be used in zone 1 ROP. (Eur J Ophthalmol 2008; 18: 112-7)*

KEY WORDS. *Retinopathy of prematurity, Diode laser photocoagulation, Cryotherapy*

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INTRODUCTION

Both transscleral cryotherapy and transpupillary diode laser photocoagulation have been shown to be effective in the treatment of threshold retinopathy of prematurity (ROP) (1-9). Cryotherapy, studied extensively as a treatment for threshold ROP in a large cohort of neonates in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity, was found to reduce the risk of an unfavorable outcome in threshold ROP from 45.4% in the untreated group to 26.1% in the treated group (2). In recent years, laser photocoagulation has gained increasing popularity for the treatment of threshold ROP (5, 6, 13).

Each modality has its particular advantages and disadvantages. The effectiveness of cryotherapy was proven in the largest multicenter randomized controlled trial of ROP treatment to date (1, 2). A mean of only 50 applications were required to ablate the avascular retina, depending on the location (zone) of ROP (1). Treatment is not hindered by decreased media clarity to the same extent as transpupillary laser photocoagulation. However, cryotherapy can cause considerable damage to nontarget tissues

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such as the conjunctiva, sclera, choroid, and macula (3, 10, 11). Beyond potential long-term sequelae, such damage may be acutely associated with more inflammation and pain, requiring general anesthesia to be administered to frail infants (1). Cryotherapy is difficult to apply to the posterior retina and may require opening the conjunctiva (1-9).

Laser photocoagulation is effective as cryotherapy in decreasing unfavorable anatomic outcomes from ROP (3-9). In addition, tissue destruction is more localized, and many studies report better postoperative visual acuity (3, 4, 9, 12) compared with cryotherapy as well as a lower incidence and severity of myopia (12, 13). Laser treatment is easier to apply to the posterior retina than is cryotherapy. However, transpupillary photocoagulation is more difficult to apply anteriorly, especially in the presence of a small pupil or unclear media, typically caused by limbal corneal pannus, tunica vasculosa lentis, or vitreous haze. A mean number of 900 to 1,600 laser applications are required to ablate the avascular retina (3, 4); therefore, treatment duration may be prolonged compared with that of cryotherapy, possibly with greater stress on the infant or requiring longer anesthesia. Laser energy is transmitted through the ocular media with an attendant risk of cornea, iris, or lens burns (15). In addition, it has recently been postulated that when a large number of burns are required to treat posterior disease, anterior segment ischemia may occur, resulting in an extremely poor visual prognosis (16).

Combining the use of laser photocoagulation with cryotherapy for the treatment of threshold ROP may provide complementary advantages of each modality while tempering the disadvantages of each. Cryotherapy could be used to treat anteriorly and laser to treat posteriorly, with greater technical ease, shorter treatment duration, and perhaps decreased risk of cataract or anterior segment ischemia. To our knowledge, such combination therapy has only been reported once before (18). We report our experience with the safety, efficiency, and effectiveness of combining cryotherapy and diode laser photocoagulation for the treatment of threshold ROP.

METHODS

In this retrospectively analyzed case series, the medical records of all patients treated for threshold ROP between January 1995 and December 2003 were reviewed, and 94 cases with combined laser + cryo treatment were identified. Mean gestational age was 26.7±2 weeks (range, 23 to 33), and mean birthweight was 865±132 g (range, 580 to 1350 g). Mean postnatal age at the time of treatment was 10±1.5 weeks (range, 8 to 13), corresponding to a mean postconceptional age at treatment of 36.5±1.3 weeks (range, 33 to 39). All treated eyes had threshold ROP as defined by the International Committee for the Classification of Retinopathy of Prematurity (19). Fifty-four eyes had threshold zone 1 disease, and the remaining 118 eyes had a mean of 8±3 clock hours (range, 7 to 12) of stage 3+ disease in posterior zone 2. For purposes of comparison with other reports, Snellen visual acuity was estimated from fixation behavior using the criteria applied by Paysse et al (3) and White and Repka (5). Cryotherapy was applied to the avascular retina as far posteriorly as possible without opening the conjunctiva. In all patients, a posterior row of cryotherapy was applied 360° using red reflex monitoring. Additional cryotherapy was placed anteriorly with indirect ophthalmoscopy visualization. Generally two rows or approximately 20 applications were necessary. Skip areas between cryotherapy spots were filled in with laser application. Diode laser photocoagulation was then applied to the remaining area of the avascular retina, titrated to a grey–white burn (200 to 500 mW, 0.5 seconds for all patients).

Patient demographics and treatment parameters are summarized in Tables I and II.

Safety was assessed by reviewing ocular and systemic complications. Efficiency was assessed by recording treatment duration and number of laser burns required, by fundus examination, visual acuity, and refraction at the most recent follow-up visit. Using criteria defined by the Cryotherapy for Retinopathy Prematurity Cooperative Group Study (2), an unfavorable outcome was defined as

TABLE I - DEMOGRAPHICS, COMBINED PROCEDURE LASER + CRYO

	Laser + cryo (n = 94 patients)		
	Mean	**Minimum**	**Maximum**
EGA (wk)	26.7	23.0	33.0
Birthweight (g)	865.0	580.0	1350.0
PCA-ROP onset (wk)	33.8	29	37
PCA-threshold (wk)	36.5	31.5	41.0

TABLE II - TREATMENT PARAMETERS COMBINED PROCEDURE LASER + CRYO

	Laser			Cryo		
	Mean	**Minimum**	**Maximum**	**Mean**	**Minimum**	**Maximum**
Number of spots	132	80	355	42.3	12	67
Power (mW)	278	200	500			
Duration (ms)	500	500	500			

TABLE III - ANATOMIC OUTCOME (N = 172 EYES)

Anatomic outcome	No. (%)
Normal posterior pole	127 (72.5)
Straightened temporal vessels	8 (4.7)
Macular ectopia	7 (4.1)
Abnormal macular pigmentation	7 (4.1)
Stage IVb	9 (5.2)
Stage V	10 (5.8)

1) a posterior retinal fold, 2) a retinal detachment involving zone 1 of the posterior pole, or 3) a retroretinal tissue or mass obscuring the view of the posterior pole. Visual acuity outcomes were defined as favorable if estimated visual acuity was better than 20/200 or unfavorable if visual acuity was less than 20/200.

RESULTS

Patients were followed up for a mean of 6.53±4.38 years (range, 4 to 11 years) after surgery. All patients experienced transient conjunctival injection and chemosis, but no other ocular complications were noted.

Treatment required a mean of 33±11 minutes/eye (range, 21 to 53) - including all examinations and interruptions - from the time the patient received sedation until the eyelid speculum was removed. The treatment time per eye for bilaterally treated patients was estimated by dividing the total documented time by two. A mean of 132±74 laser burns (range, 80 to 355) were required after cryotherapy to achieve near-confluent ablation of the avascular retina.

The findings at the patients' most recent dilated fundus examination are summarized in Table III. Using the criteria defined by the Cryotherapy for Retinopathy of Prematurity Cooperative Group (2), a favorable outcome was achieved in 149 of 172 eyes (87%).

TABLE IV - FUNCTIONAL OUTCOME AT FINAL EXAMINATION (N = 172 EYES)

Functional outcome	No. (%)
Visual acuity better than 20/200	131 (76)
Vision not measured	8 (4.7)
Fixation central, steady, unmaintained	6 (3.5)
Monocular nystagmus	8 (4.7)
Hand motions only	8 (4.7)
No light perception	12 (7)

TABLE V - POSTOPERATIVE COMPLICATIONS OF COMBINED LASER + CRYO TREATMENT (N = 172 EYES)

	No. (%)
Corneal edema	12 (6.9)
Anterior segment ischemia	3 (1.7)
Posterior synechiae	7 (4)
Cataract	9 (5.2)
Hyphema	7 (4)
Vitreous hemorrhage	13 (7.5)
Retinal-choroidal hemorrhage	11 (6.3)

TABLE VI - FINAL REFRACTION (SPHERICAL EQUIVALENT) (N = 172 EYES)

	No. (%)
Hypermetropia > +6.0 D	9 (5.2)
Hypermetropia +3.0 to +6.0 D	18 (10.5)
Hypermetropia < +3.0 D	29 (17)
Myopia < –3.0 D	46 (26.7)
Myopia –3.0 to –6.0 D	44 (25.6)
Myopia > –6.0 D	26 (15.1)

Visual acuity is summarized in Table IV. In all cases, visual acuity was assessed by testing fixation behavior (20). All of the eyes with normal vision had a normal posterior pole on fundus examination.

Eight eyes did not have visual acuity documented in the chart, but all of these eyes had normal posterior pole anatomy, which has been reported to correlate well with normal visual acuity in ROP (19, 20, 22). A total of 149 of 172 measured eyes (87%) had a favorable functional outcome. Estimated visual acuity better than 20/200 was present in 131 (76%) of all analyzed eyes.

Corneal edema, vitreous hemorrhage, and retinal-choroidal hemorrhage were the main postoperative complications of combined treatment (Tab. V).

All eyes were refracted at 12 months or later. Five eyes were not refracted because of retinal detachment, and 6 eyes were not followed up until 12 months. The distribution of refractive errors is illustrated in Table VI. The mean spherical equivalent after cycloplegia using 1% cyclopentolate was –5.45±4.32 diopters (D) (range, –12.50 to +6.50 D). At final visit, 116 of 172 eyes (67.4%) were myopic, and 26 of 172 eyes (15.1%) were highly myopic (>6 diopters).

DISCUSSION

Combined use of cryotherapy and laser photocoagulation has been reported previously to be effective (18). In this study we add our experience with 94 additional patients.

Combination therapy appeared to be safe. No serious ocular or systemic complications occurred in this group of patients, although the incidence of cataract formation after transpupillary laser photocoagulation for ROP may be as high as 6% (15). Lambert et al (16) recently described 10 eyes that developed dense cataracts postulated to be secondary to anterior segment ischemia after extensive laser photocoagulation for ROP. Nine of these 10 eyes progressed to phthisis bulbi and no light perception (16). The investigators theorized that the risk of cataract may increase with the number of laser burns required, whether the cataract is caused by direct thermal injury to the lens or results from anterior segment ischemia (16). The eyes in their study required a higher number of laser burns (2532 burns) for ROP than eyes in other series, partly because of the relatively posterior location of disease (16). In our study, only 216 laser burns were required despite the posterior location of the ROP. Lambert et al (16) suggested that cryotherapy be added to the treatment regimen when ROP is located relatively posteriorly because freezing causes less damage to ocular vessels than does photocoagulation (16). A rabbit model developed by Freeman et al (17) also suggests that cryotherapy is less likely to produce anterior segment ischemia than photocoagulation (17).

As noted by Azad et al (22), cryotherapy is less time consuming than laser photocoagulation in that a much larger area of retina is ablated per application. We estimate that 50-diode laser burns are necessary to cover the same retinal area covered by one cryotherapy application. Using cryotherapy alone requires only 40 to 50 applications per eye (1, 3), whereas studies using laser alone reported a mean number of 956 to 1556 burns required (3, 14). Treatment of our patients required a mean 132 laser burns/eye after cryotherapy. Therefore, using laser alone is likely more time consuming than combination therapy, which may lead to longer anesthesia time and greater risk of laser-related complications.

The favorable anatomic outcome rate was 87%, which compares favorably with results reported after cryotherapy alone (74.3%) or laser alone (91.6%) (8). The favorable functional outcome rate was 76%, which also compares well with results reported after cryotherapy alone (65%) (2). Some studies suggest superior visual acuity outcomes after laser photocoagulation compared with cryotherapy, but these studies are either small or do not compare concurrently treated groups (nonrandomized) (3-5). Potentially confounding variables include 1) the possibility of an effect on the overall improvement in the systemic management of premature infants during the time period of these studies and 2) a different length of follow-up between groups.

The studies by the Cryotherapy for Retinopathy of Prematurity Cooperative Group reported that functional outcome is strongly correlated with visible posterior pole changes (21). Macular pigment changes associated with markedly decreased vision have been reported in 10% to 34% of eyes after cryotherapy for ROP (3, 11). We observed macular pigmentary change in seven eyes, possibly because we did not apply cryotherapy as far posteriorly or to as large an extent as described in one of the reports (11).

The high incidence of myopia (67.4%) and severity of myopia (15.1% incidence of myopia >6 diopters) in this study are similar to what others have reported after using cryotherapy alone (2, 13, 23). Two groups of investigators have reported, in small nonrandomized studies, that cryotherapy is associated with a higher incidence and severity of postoperative myopia than is laser treatment (12, 13).

Patients in this study may have been predisposed to severe myopia because of the posterior location of their ROP. It is well recognized that incidence and severity of myopia correlate with severity of ROP regardless of the treatment modality employed. There is selection bias in this study toward eyes with more posterior disease because more eyes with anterior disease were treated with cryotherapy alone rather than combination therapy.

In conclusion, combined cryotherapy and diode laser photocoagulation for ROP in our patients resulted in regression of threshold ROP with relatively successful structural and functional outcomes. Combined therapy may be faster and useful for eyes with very posterior ROP. This may decrease the number of complications occurring when excessive cryotherapy or laser photoablation must be used in zone 1 ROP.

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