

A Comparison of Dense versus Less Dense Diode Laser Photocoagulation Patterns for Threshold Retinopathy of Prematurity

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Objective: To determine if the density of diode laser photocoagulation for the treatment of zone 1 or zone 2 threshold retinopathy of prematurity (ROP) affects the rate of progression of the disease.

Design: Retrospective, nonrandomized, comparative trial (n = 12) and prospective, randomized, clinical trial (n = 46).

Participants: Two surgeons treated a total of 107 eyes from 58 patients with zone 1 or zone 2 threshold ROP within 72 hours of diagnosis. The two consecutive groups of patients were treated with two different diode laser photocoagulation patterns between May 1995 and October 1997 and were observed for at least 3 months.

Intervention: All patients underwent diode laser photocoagulation of the peripheral avascular retina extending from the ridge of extraretinal proliferation to the ora serrata. One cohort received a near confluent laser pattern, whereas the second cohort received a pattern of laser spots placed 1 to 1.5 burn widths apart.

Main Outcome Measures: Anatomic outcome, rate of progression to stage 4 or 5 retinopathy of prematurity, postoperative complications, and timing and frequency of retreatment.

Results: For analysis, the retrospective and randomized outcome data were grouped. The rate of progression in the near confluent laser treatment group was 3.6% overall, 0% of zone 1 eyes, and 3.8% of zone 2 eyes. The rate of progression in the less dense treatment group was 29% overall, 44% of zone 1 eyes, and 21% of zone 2 eyes. Mean time to retreatment was 16 days in cohort 1 and 24 days in cohort 2.

Conclusions: A dense pattern of diode laser treatment for threshold ROP and prompt retreatment for residual plus disease significantly reduce the rate of progression in eyes with zone 2 disease ($P = 0.02$) and may be beneficial in eyes with zone 1 disease. *Ophthalmology* 2000;107:324–328 © 2000 by the American Academy of Ophthalmology.

The Cryo-ROP study was a multicenter, prospective, randomized clinical trial that demonstrated that cryotherapy reduces the risk of an unfavorable outcome for eyes with threshold retinopathy of prematurity (ROP), defined as Stage 3+ disease in zone 1 or zone 2, with 5 or more contiguous or 8 cumulative clock hours of extraretinal fibrovascular proliferation.^{1–3} At 3 months, 43% untreated versus 22% treated eyes had unfavorable structural outcomes.

Diode laser photocoagulation with indirect ophthalmoscopic delivery has become the preferred method for treating threshold ROP.^{4–13} The density of diode laser spots

used in previous reports ranges from one-quarter burn width to 1 burn width apart, typically extending from the ridge of extraretinal fibrovascular proliferation to the ora serrata.

To our knowledge, no report to date has answered the question, “Does the density of the laser pattern to the avascular peripheral retina affect disease progression in threshold ROP?” Our study evaluated this issue through an analysis of consecutive eyes reaching threshold ROP, treated using diode laser photocoagulation by one of two methods: a dense, near confluent laser pattern, or a less dense pattern with burns spaced 1 to 1.5 burn widths apart.

Methods

A retrospective chart review was performed on consecutive patients who underwent laser therapy by one of two surgeons (PJF and MTT) from May 1995 through November 1997. Institutional Review Board approval from the William Beaumont Hospital (WBH) committee was obtained. A total of 127 eyes were identified that were diagnosed with threshold ROP and treated with indirect diode laser photocoagulation within 72 hours of diagnosis. Eyes with less than 3 months of follow-up or with a history of previous laser or cryotherapy were excluded. Eyes diagnosed with stage 4 or 5 ROP, or any other ocular disorder other than ROP, were excluded. One hundred seven eyes of 58 patients were eligible for the study.

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Table 1. Patient Data and Results

Data	All Eyes (n = 107)	Cohort 1 (n = 56)	Cohort 2 (n = 51)
Mean post conception age (wks)	38.0	38.1	37.9
Mean birth weight (g)	787	751	843
Mean gestational age (wks)	25.9	25.7	26.1
No. eyes zone 1 (%)	22/107 (20.6)	4/56 (7.1)	18/51 (35.3)
No. eyes zone 2 (%)	85/107 (79.4)	52/56 (92.9)	33/51 (64.7)
Mean no. clock hours of threshold	6.7	6.2	7.3
Mean laser spot count			
Zone 1	712	1253	592
Zone 2	577	649	457
Total	606	693	508
No. of eyes with progression (%)			
Zone 1	8/22 (36.4)	0/4	8/18 (44.4)
Zone 2	9/85 (10.6)	2/52 (3.8)	7/33 (21.2)
Total	17/107 (15.9)	2/56 (3.6)	15/51 (29.4)

Cohort 1 = eyes treated with near confluent laser pattern; Cohort 2 = eyes treated with burns spaced 1 to 1.5 burn widths apart.

All preterm infants at WBH weighing less than 1500 grams or with a gestational age of less than 32 weeks were screened by either one of two authors (Philip J. Ferrone or Michael T. Trese). Screening at Children's Hospital of Michigan (CHM) and St. John's Hospital (SJH) was performed by pediatric ophthalmologists, who referred most patients with threshold ROP to one of the authors (Michael T. Trese) for evaluation. Twenty-one eyes of 12 patients were diagnosed and treated at either CHM or SJH. Infants were examined 4 to 6 weeks after delivery and at biweekly intervals thereafter until retinal vascular maturation. If prethreshold disease (zone 1 any stage, zone 2 with stage 2 plus disease, or zone 2 with stage 3 plus disease with less than 5 contiguous or 8 total clock hours of stage 3) was reached, weekly examinations were performed. A complete ocular examination including indirect ophthalmoscopy with scleral depression using a Flynn lens loop was performed. Examinations were recorded on a standardized data sheet. Zones 1, 2, and 3 were defined according to the Committee for the Classification of Retinopathy of Prematurity. Informed consent from a legal guardian was obtained in all cases. If both eyes reached threshold concurrently, both eyes were treated similarly in the same session. At WBH, randomization to one of the two treatment cohorts for 46 of the 58 patients was performed by our surgical coordinator and was based on surgeon and operating room availability at WBH within 72 hours of threshold ROP diagnosis. The 12 patients treated at CHM and SJH were assigned to cohort 2 in all cases and were not randomized.

A portable diode laser with an indirect delivery system (IRIS Medical Inc., Mountainview, CA), a lid speculum, a 28 diopter (D) Volk (Mentor, OH) or Nikon (Melville, NY) aspheric hand-held condensing lens, and a Flynn lens loop (Storz Inc., St. Louis, MO) were used in all treatments. Laser treatment was applied to the avascular retina immediately anterior to the ridge of extraretinal fibrovascular proliferation extending to the ora serrata for 360° in all cases. A moderate white burn was the target intensity for both surgeons. Laser settings were varied to achieve the desired lesion intensity, but ranged from a 150 mW to 400 mW and 0.2 to 0.3 seconds. Cohort 1 was comprised of eyes treated with a near confluent laser pattern by one surgeon, and cohort 2 included eyes treated by another surgeon with laser burns spaced 1 to 1.5 burn widths apart.

Follow-up examinations were performed weekly until regression of plus disease and extraretinal fibrovascular proliferation had occurred, then every 2 to 4 weeks until 3 months of age (corrected). Supplemental laser treatment was performed if skip areas were identified and plus disease persisted for 2 weeks or more after the initial treatment.

Progression was defined as the development of stage 4A, 4B, or 5. A progressive 4A detachment of greater than 3 ridge widths in extent was categorized as progression for the purpose of this study. Eyes with stage 4A detachments that were limited in width and spontaneously regressed were not categorized as progression.

Statistical analysis of the data was performed using Statview (Abacus Concepts, Inc., Berkeley, CA). The mean postconceptional age (PCA), birth weight (BW), gestational age (GA), and clock hours of stage 3 were compared using unpaired *t* tests. Categorical data such as disease progression were analyzed using contingency tables and Fisher's exact test.

Results

A total of 107 eyes from 58 patients met the criteria for inclusion. The retrospective (n = 12) and randomized (n = 46) patients were grouped for analysis. Twenty-seven patients were female, and 31 were male. There were 53 right eyes and 54 left eyes. The mean PCA at the time of treatment was 38 weeks, ranging from 32.5 to 46 weeks. The mean GA at delivery was 25.9 weeks, ranging from 23 to 32 weeks. Birth weights ranged from 365 to 1350 grams, with a mean of 787 grams. Twenty-two eyes had zone 1 ROP, and 85 eyes had zone 2 ROP. The mean number of clock hours of stage 3 ROP was 6.7, ranging from 5 to 12. The mean number of laser spots used per eye was 606, ranging from 130 to 1860 spots. There were 39 eyes from 22 patients that received supplemental laser treatment. The mean interval between the first and second laser treatments was 19.4 days, ranging from 5 to 42 days. One patient in cohort 1 received laser treatment for zone 1 ROP in two sessions, 5 days apart, to allow regression of a prominent tunica vasculosa lentis. Follow-up ranged from 90 to 841 days, with a mean of 387 days.

Table 1 provides a comparison of the patient populations comprising cohort 1 and cohort 2. For eyes in cohort 1, the mean number of laser spots was 649 (range, 130 to 1860) in the zone 2 eyes and 1253 (range, 1028 to 1390) in the zone 1 eyes. The average amount of extraretinal fibrovascular proliferation was 6.2 clock hours. Two of 56 eyes (3.6%) progressed to stage 4A retinal detachments that were progressive. Both eyes had zone 2 disease, and both eyes had supplemental laser therapy.

For eyes in cohort 2, the mean number of laser applications was 457 (range, 291 to 810) for zone 2 eyes and 592 (range, 295 to 861) for zone 1 eyes. There was an average of 7.3 clock hours of stage 3 disease. A total of 15 of 51 eyes (29.4%) progressed to stage 4 or 5 ROP. Eight eyes had zone 1 disease, and 7 eyes had

zone 2 disease. Of the eyes that progressed, 8 eyes developed progressive stage 4A detachments, and 6 eyes had stage 4B detachments. One patient was lost to follow-up for 6 months after laser treatment and had a stage 5 open funnel retinal detachment in the treated eye at presentation. Of the 15 eyes that progressed, 7 eyes received supplemental laser treatment.

The overall differences in the mean PCA and GA at treatment between the two cohorts were not significant; however, the patients in cohort 1 had significantly lower mean birth weights than patients in cohort 2: 751 grams versus 843 grams, respectively ($P = 0.05$). Overall, there was a highly significant difference in the mean number of laser spots between the two cohorts: 693 in cohort 1 and 508 in cohort 2 ($P = 0.0007$). Overall, the mean number of clock hours of stage 3 disease was significantly higher in cohort 2 than in cohort 1: 7.3 versus 6.2 ($P = 0.007$). There was no significant difference in the number of eyes receiving supplemental laser treatments between cohort 1 and cohort 2: 21 of 56 eyes (37.5%) versus 18 of 51 eyes (35.3%). However, eyes in cohort 1 that received supplemental laser treatment were treated much earlier than those in cohort 2, with a mean of 16 days compared with 24 days ($P = 0.02$).

When comparing the 17 eyes that progressed with eyes that did not progress, there were no statistically significant differences in mean PCA at the time of treatment, BW, and GA. The difference in the mean number of clock hours of stage 3 ROP was not statistically significant between eyes that progressed and eyes that did not progress: 7.7 versus 6.5, respectively ($P = 0.057$). For eyes that did progress, cohort 1 had a mean of 6.5 clock hours of stage 3 disease compared with 7.9 clock hours in cohort 2 ($P = 0.56$).

For eyes with zone 2 disease, 2 of 52 eyes (3.8%) in cohort 1 progressed compared with 7 of 33 eyes (21.2%) in cohort 2 ($P = 0.02$). There were no statistically significant differences in PCA, BW, or GA between the two populations. Zone 2 eyes in cohort 2 had a significantly greater mean number of clock hours of stage 3 disease compared with cohort 1 (7.2 versus 6.3); ($P = 0.03$). There was a highly significant difference in the mean number of laser spots placed between the two cohorts for zone 2 eyes: 649 in cohort 1 and 457 in cohort 2 ($P = 0.002$).

For eyes with zone 1 disease, 0 of 4 eyes in cohort 1 and 8 of 18 eyes (44.4%) in cohort 2 progressed after treatment. Patients in cohort 1 had significantly lower average birth weights than those in cohort 2: 608 grams versus 823 grams ($P = 0.02$). Patients in cohort 1 had a mean GA of 23.8 weeks compared with 25.6 weeks in cohort 2 ($P = 0.005$). There was a highly significant difference in the mean number of laser spots for zone 1 eyes between groups: 1253 spots in cohort 1 and 592 in cohort 2 ($P \leq 0.0001$). When comparing the proportion of eyes with zone 1 ROP between cohort 1 (4 of 56 eyes) and cohort 2 (18 of 51 eyes), the difference was highly significant ($P = 0.0006$).

Zone 1 threshold ROP was associated with a significantly greater risk of progression to retinal detachment after laser treatment than eyes with zone 2 disease ($P = 0.007$). Eyes in zone 1 had a significantly higher number of supplemental laser treatments (14 of 22 eyes; 63.6%) compared with those in zone 2 (25 of 85 eyes; 29.4%; $P = 0.0054$).

After the exclusion of 12 patients in cohort 2 who were not randomized, the difference in progression for the 46 randomized patients was statistically significant: 2 of 56 eyes (3.6%) in cohort 1 and 6 of 29 eyes (20.7%) in cohort 2 ($P = 0.02$).

There were no significant differences in treatment complications between the two cohorts. There were no cases of cataract or iris burns detected in any of the laser treated eyes on follow-up examination. Preretinal hemorrhage occurred in 12 of 107 eyes treated with laser. Seven of these 12 hemorrhages occurred in eyes that ultimately progressed to stage 4A or 4B ROP. Five of the 12

Table 2. Series of Consecutive Eyes with Threshold Retinopathy of Prematurity Treated with Diode Laser Photocoagulation*

Series	Regression
Tsitsis et al ⁸	27/31 eyes (87%)
McNamara et al ⁹	25/28 eyes (89%)
Hunter et al ¹⁰	16/17 eyes (94%)
Seiberth et al ¹¹	25/25 eyes (100%)
Benner et al ¹²	9/9 eyes (100%)
Goggin et al ¹³	16/21 eyes (76%)
Cohort 1	54/56 eyes (96%)
Cohort 2	36/51 eyes (71%)

* All eyes have at least 3 months follow-up

hemorrhages were extramacular and cleared spontaneously. In some infants bradycardia occurred during laser treatment that resolved promptly after temporary suspension of treatment in all cases.

Discussion

The difference in diode laser photocoagulation patterns used by two surgeons with large pediatric patient populations provides a unique opportunity to compare the structural outcomes of a large number of patients treated over a 2.5-year period. Most of our patients (86 eyes) were randomly treated by one of two surgeons at WBH and received comparable screening, preoperative, perioperative, and postoperative care. One 810-nm diode laser was used for all treatments by both surgeons. The Cryo-ROP study demonstrated a strong correlation between structural outcome at 3 months and longer term structural outcome.¹⁻³ The mean follow-up in our study was slightly over 1 year with a minimum of 3 months.

Our study represents the largest reported consecutive series of patients with threshold ROP treated with diode laser photocoagulation. The difference in the overall rate of progression of cohort 1 (2 of 56 eyes; 3.6%) compared with cohort 2 (15 of 51 eyes; 29.4%) was highly significant ($P = 0.0003$). The rate of progression of 3.6% in cohort 1 compares favorably with previously reported outcomes (Table 2).⁹⁻¹³ In addition to the difference in laser pattern density, retreatment occurred a mean of 8 days earlier in cohort 1 than in cohort 2: 16 and 24 days, respectively. Dense initial laser treatment (Fig 1) and prompt retreatment for the presence of any residual plus disease may be the principal interventions accounting for the favorable results in cohort 1.

Eyes with zone 2 disease were analyzed independently and demonstrated significantly less progression in the dense treatment group compared with the less dense treatment group (3.8% vs. 21.2%). There were no significant differences in patient characteristics between these two groups, except that the mean number of clock hours of stage 3 disease was less in cohort 1 than cohort 2 (6.2 vs. 7.3). This is unlikely to produce the pronounced difference in structural outcomes found in our study. The low number of zone 1 eyes in cohort 1 precludes meaningful comparisons in this

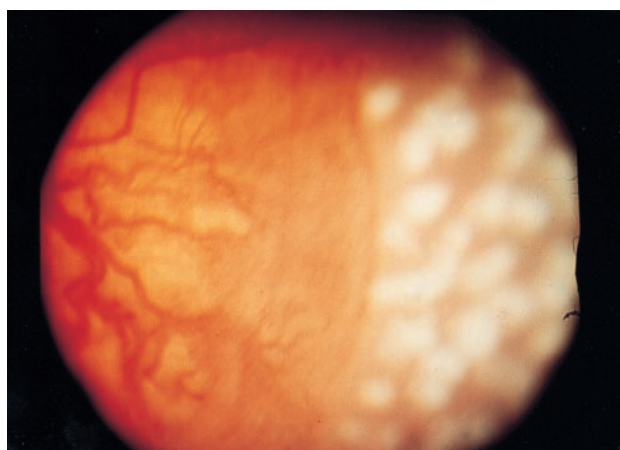


Figure 1. Representative actual dense laser treatment pattern used in cohort 1 to treat threshold retinopathy of progression.

subgroup; however, the 8 of 18 eyes (44.4%) that progressed in cohort 2 (less dense treatment group) compares favorably with the 75% of zone 1 eyes with unfavorable outcome in the Cryo-ROP study.

A weakness of our study design, other than combining retrospective and prospective data, is the possibility that an undetected difference between the two cohorts exists that selectively predisposed patients in cohort 2 to zone 1 ROP or disease progression. There is a significant disparity in the number of eyes classified into zone 1 between cohort 1 and cohort 2 over the same period (4 vs. 18 eyes, respectively). Possible explanations for these data include the presence of 22 eyes from 12 patients who were in cohort 2, all of whom had undergone preoperative, perioperative, and postoperative care at an institution other than WBH. Of these 22 eyes, 9 had zone 1 (5 patients) and 13 had zone 2 (7 patients) ROP. Five of the 9 eyes in the zone 1 subgroup progressed, and 4 of the 13 eyes in the zone 2 subgroup progressed. Factors including oxygen administration, indomethacin, or surfactant use reportedly associated with ROP¹⁴⁻¹⁷ were not controlled for at these outside hospitals and may have some role in the aggressiveness of the ROP in this population. However, these patients represent a small fraction of the total number of eyes in our study (20.5%). When these eyes are excluded from our analysis, there is still a significantly higher rate of progression in cohort 2 compared with cohort 1: 20.7% versus 3.6%, respectively ($P = 0.012$).

Despite the retrospective nature of portions of our study and the inability to control for systemic parameters that may play a role in determining ocular morbidity in ROP, our data show a significant treatment benefit for eyes with zone 2 ROP treated with a near confluent laser pattern and prompt retreatment in the presence of residual plus disease. Although the number of zone 1 eyes was too small to reach statistical significance, dense laser treatment in these eyes seems indicated based on our results. A larger, multicentered, prospective, randomized clinical trial is needed to clarify this issue further. One would need 422 eyes to detect

a 10% difference in the rate of progression between the two study groups (95% confidence interval).

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