Pulsed mode versus near-continuous mode delivery of diode laser photocoagulation for high-risk retinopathy of prematurity

Evelyn A. Paysse, MD,[a,b] Mohamed A.W. Hussein, MD,[a] Aaron M. Miller, MD,[a] Kathryn M. Brady McCreery, MD,[a] and David K. Coats, MD[a,b]

OBJECTIVE To compare structural and functional outcomes and efficiency of diode laser photocoagulation for retinopathy of prematurity (ROP) when delivered in a pulsed mode versus a near-continuous mode.

METHODS A retrospective study was conducted of 138 patients who underwent diode laser photocoagulation for threshold ROP using either pulsed or near-continuous delivery. Laser-related complications and structural and functional outcomes were analyzed. Prospectively, time efficiency and total energy used were evaluated in nine infants with bilateral symmetric high-risk prethreshold ROP in which one eye of each infant was randomized to pulsed and the fellow eye to near-continuous delivery.

RESULTS There was no significant difference between groups with regards to prevalence of posterior disease (Zone 1 or posterior Zone 2) ($p = 0.11$), postoperative vitreous haze ($p = 0.60$), postoperative complications ($p = 0.38$), retinal detachment ($p = 0.90$), strabismus ($p = 0.73$), amblyopia ($p = 0.69$), or refractive error ($p = 0.95$). Mean time for treatment was 23 minutes using pulsed delivery versus 14 minutes per eye with near-continuous delivery ($p < 0.001$). The mean total power used per eye with pulsed mode delivery was 1.5×10^5 W versus 1.1×10^5 W with near-continuous delivery ($p = 0.015$).

CONCLUSIONS No differences in complications, functional outcome, or structural outcome were found between using pulsed mode and near-continuous mode diode laser delivery for high-risk ROP. Near-continuous laser delivery, in our hands, was more time-efficient and used less total power. (J AAPOS 2007;11:388-392)

Retinopathy of prematurity (ROP) remains one of the most common causes of childhood blindness.[1] Photocoagulation to the peripheral avascular retina was the first proposed treatment for the management of threshold ROP,[2] but, because of difficulty with the laser delivery system at that time, laser treatment was soon supplanted by cryotherapy.[3] With improvement in laser delivery systems, photocoagulation reemerged as a viable method for ablating the peripheral avascular retina in infants with severe ROP. Transpupillary diode laser photocoagulation has proven to be as safe and at least as effective as cryotherapy.[4-6] Diode laser photocoagulation is now the preferred method by most ophthalmic surgeons who treat ROP.[4,7-9]

The effectiveness of diode laser photocoagulation in the management of severe ROP has been evaluated and compared when the laser energy is delivered in a dense (or confluent) versus a less dense pattern,[10,11] and when using a trans-scleral versus a transpupillary approach.[9] No study, however, has compared the results of treatment when laser energy is delivered in a pulsed mode versus a near-continuous mode. Potential advantages of near-continuous mode delivery are increased time efficiency leading to less anesthetic/sedative medication requirements, better uptake of laser energy with varying retinal thickness and pigmentation, and more complete treatment. The purpose of this study was to compare the structural and functional outcomes and time for treatment of diode laser photocoagulation when delivered in a pulsed mode versus a near-continuous mode.

Patients and Methods

This two-part retrospective and prospective study was approved by the Institutional Review Board of Baylor College of Medicine. A retrospective study was conducted of consecutive patients who underwent diode laser photocoagulation for threshold ROP over a 4-year period. Eligible patients were identified through a log-

[a]*Author Affiliations:* [a]*Cullen Eye Institute, Baylor College of Medicine, Department of Ophthalmology, Texas Children's Hospital, Houston, Texas; and* [b]*Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas*

Presented at the Association for Research in Vision and Ophthalmology, April 2004, Ft. Lauderdale, Florida.

This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Dr. Evelyn Paysse had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Submitted April 20, 2006.

Revision accepted November 4, 2006.

Reprint requests: Evelyn A. Paysse, MD, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin MC CC 640.00, Houston, TX 77030 (email: epaysse@bcm.tmc.edu).

1091-8531/2007/$35.00 + 0

doi:10.1016/j.jaapos.2006.11.011

book of laser-treated ROP patients. To be eligible for inclusion, the infants had to have received diode laser treatment for threshold ROP and have a birth weight of less than or equal to 1500 g and/or an estimated gestational age (EGA) of less than or equal to 28 weeks, consistent with the screening recommendations at that time developed by the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Pediatrics.[12] Follow-up examinations that included visualization of the fundus at 1 week, 2 weeks, 3 to 4 weeks, and 9 to 12 weeks following treatment were required to be included in the retrospective part of the study. ROP was classified using the International Classification of Retinopathy of Prematurity with the addition of a division of Zone 2 into anterior and posterior zones as it has been shown that posterior Zone 2 ROP behaves more like Zone 1 ROP.[11,13]

The ROP treatment protocol during the years under study consisted of application of diode laser photocoagulation (Iridex, Oculight GL, Mountain View, CA) to the entire peripheral avascular retina with gray-white intensity burns separated by no more than one-half spot size. We used either a 300 ms pulse duration or a near-continuous mode laser application placed in such a way as to simulate individual laser spot applications. To simulate individual spots using the near-continuous mode delivery, the diode laser duration was set at 9000 ms and an interval of 50 ms. The interval is the period of pause between laser energy deliveries. The power was set to start at 180 mW, which was increased if needed until the desired gray-white burn was achieved. For the pulsed mode, the interval was 50 ms. To create separated spots with the near-continuous mode delivery, the treating surgeon moved the laser beam to adjacent areas of retina at an appropriate speed, so areas of interruption between laser burns would occur (Figure 1). Depending on laser uptake in different parts of the retina, the laser beam was moved at varying rates, thus avoiding the need for frequent adjustment of the power setting during the treatment. With pulsed mode laser treatment, the treating ophthalmologist adjusted the power up or down as needed throughout the procedure to achieve the appropriate burn intensity. The mode of laser delivery was determined by physician preference (ie, both treatments were done throughout the 4-year study period). For each treatment group, the data analyzed included EGA, birth weight, parameters of laser treatment (power, duration of laser pulse, and number of pulses per eye), and number of eyes treated for each zone (Zone 1, posterior Zone 2, or anterior Zone 2).

The following laser-related complications were compared between treatment groups: vitreous hemorrhage, cataract, iris burns, corneal stromal haze, iridocorneal adhesions, glaucoma, inadvertent laser burns, and hypotony. The retinal and anterior segment examination results were analyzed for each treated eye during the first 4 weeks after surgery and again at 9 weeks and 6 months following treatment. Poor structural outcome was determined if an eye developed a retinal detachment or severe macular ectopia/fold. Functional outcomes, including visual behavior, refractive error, and the presence of strabismus or amblyopia, were evaluated 6 months after laser treatment and compared between the two treatment groups.

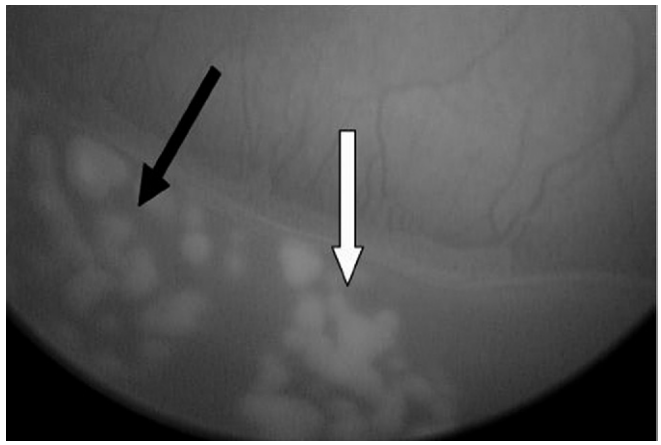

FIG 1. Retina with high-risk prethreshold ROP demonstrating the near-continuous mode laser result (black arrow) and the pulsed mode laser result (white arrow) adjacent to each other. Note that the treatments appear very similar with a clear area between spots of laser uptake. This patient was not a participant in the prospective cohort of this study.

To assess time efficiency, we prospectively evaluated pulsed versus near-continuous laser treatment in nine infants requiring laser for bilateral symmetric high-risk prethreshold ROP. One eye of each infant was randomized using a random number generator to treatment with pulsed mode laser delivery, and the fellow eye was treated with near-continuous mode laser. Time for treatment and total energy used were compared. Total energy used was calculated by multiplying power by number of spots by duration of pulse.

For the retrospective part of the study, the χ^2 test was used to indicate possible associations between treatment modality and each outcome or complication. Odds ratios (ORs), 95% confidence intervals (CIs), and p = values were estimated for each outcome variable. The paired t-test was used to compare the mean spherical equivalent refractive error between the two treatment groups. For the prospective part of the study, the paired t-test was used to compare the time for treatment and the Wilcoxon signed ranks test was used to compare total power between the treatment groups. Significance was established at $p \leq 0.05$.

Results

A total of 293 eyes of 154 patients underwent transpupillary diode laser photocoagulation for threshold ROP during the period under evaluation for the retrospective part of the study. Eyes were excluded from analysis if they had a follow-up of less than 9 weeks after surgery and when the mode of laser delivery was not recorded or not clear. Following these exclusions, a total of 266 eyes of 138 patients remained for analysis. No patient required retreatment in either group.

Table 1 summarizes baseline characteristics and laser parameters for each treatment group. Twenty eyes (14.1%) in the pulsed mode group versus 10 eyes (8%) in the near-continuous mode group had either Zone 1 or posterior Zone 2 threshold ROP (ie, posterior ROP) at the time of treatment ($p = 0.11$).

Table 1. Baseline characteristics and laser parameters in each treated group

Variable	Pulsed mode	Near-continuous mode	*p*-value
No. of eyes treated	141	125	N/A
Male:female	31:41	23:43	0.32
Right eyes	77 (54%)	67 (54%)	0.87
Mean EGA (wk)	25.4 (23-29)	25.8 (22-30)	0.25
Mean birth weight (g)	737 (300-1157)	781 (301-1361)	0.27
No. of eyes with posterior disease	20 (14%)	10 (8%) (1-2)	0.11
Mean power (mW)	307 (185-800)	256 (158-800)	<0.001
Duration (ms)	310 (300-500)	9000	<0.001
Mean no. of spots	1532 (575-2900)*	100 (20-519)*	<0.001

EGA: estimated gestational age.
*The large difference in number of spots delivered is because near-continuous laser duration is 9000 ms versus 300 ms for the pulsed-mode delivery.

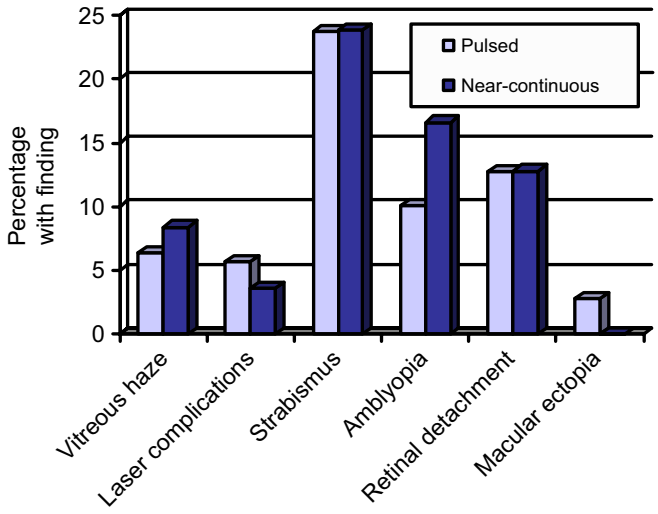

FIG 2. Functional and structural outcomes and direct laser-related complications in the two treatment groups. There was no significant difference in any of these comparisons.

Laser-Related Complications

Two hundred sixty-six eyes (138 patients) were evaluated for complications. Poor view and vitreous hemorrhage/haze were encountered during the first week in 10 (7%) eyes treated with pulsed mode laser and in 11 (9%) eyes treated with near-continuous mode laser [OR 0.75; 95% CI (0.3-2.1); $p = 0.6$]. Complications encountered in the pulsed mode group included cataract (1 eye), vitreous hemorrhage (2 eyes), iris burns (2 eyes), hyphema (2 eyes), and corneal stromal haze (2 eyes). Complications seen in the near-continuous mode group included vitreous hemorrhage (1 eye), iris burns (1 eye), hyphema (2 eyes), and iridocorneal adhesions (1 eye). In total, nine eyes treated with pulsed mode laser (6%) and five eyes (4%) treated with near-continuous mode laser had direct laser-related complications [OR 1.64; 95% CI (0.5-5.5); $p = 0.38$] (Figure 2). Other reported diode laser related complications including inadvertent laser burns, glaucoma, and hypotony did not occur in either group. No late complications were noted at the 6-month follow-up examination in either group. The only visually significant complication was the cataract that occurred in the pulsed mode delivery group. All other complications were minimal and resolved without further intervention.

Structural Outcome

Two hundred sixty-six eyes (138 patients) were evaluated for structural outcomes. At 9 weeks, 18 (13%) eyes in the pulsed mode group had developed retinal detachment compared with 16 eyes (13%) in the near-continuous mode group [OR = 1.00; 95% CI (0.5-2.2); $p = 0.9$] (Figure 2). Four eyes (3%) developed macular ectopia in the pulsed mode group, while no eyes developed macular ectopia in the near-continuous mode group ($p = 0.12$, Fisher exact two-tailed test).

Functional Outcome

One hundred seven children were included in the 6-month functional outcomes analysis. Sixty-three (87%) of 72 infants treated with pulsed mode laser and 44 (67%) of 66 infants treated with near-continuous mode laser were evaluated for the presence of strabismus and amblyopia 6 months after treatment. Of these, 14 (22%) pulsed mode infants versus 11 (25%) near-continuous mode infants had developed strabismus [OR = 0.87; 95% CI (0.3-2.3); $p = 0.73$] (Figure 2). Seven (11%) pulsed mode infants versus six (14%) near-continuous mode infants had developed amblyopia [OR = 0.79; 95% CI (0.2-2.9); $p = 0.69$] (Figure 2).

Refractive error was evaluated in 52 right eyes treated with pulsed mode laser and 38 right eyes treated with near-continuous mode laser at the 6-month examination. The average refractive error was −2.77 D (−19.00 to +4.5 D) in the pulsed mode group versus −3.78 D (−20.00 to +3.00 D) in the near-continuous mode group ($p = 0.27$). Refractive error was evaluated in 55 left eyes treated with pulsed mode laser and 38 left eyes treated with near-continuous mode laser at 6 months. The average refractive error in these eyes was −3.48 D (−19.50 to +4.50 D) in the pulsed mode group versus −2.79 D (−21.00 to +3.00 D) in the near-continuous mode group ($p = 0.26$). The average refractive error with both eyes combined was −3.17 D (−19.50 to +4.50 D) in the pulsed mode group versus −3.22 D (−21.00 to +3.00 D) in the near continuous mode group ($p = 0.95$).

Efficiency and Power Used

In the prospective part of the study, four of the nine infants (44%) had high-risk prethreshold ROP in Zone 1 and five (55%) had high-risk prethreshold ROP in Zone 2 at the time of treatment. The mean time for treatment of an eye using pulsed mode laser delivery was 23 minutes versus 14 minutes when using near-continuous laser delivery ($p < 0.001$). The mean total power used per eye was

1.5×10^5 W for pulsed mode delivery versus 1.1×10^5 W for near-continuous delivery ($p = 0.015$). All eyes had complete regression and normal structural outcomes 6 months following treatment.

Discussion

Compared with cryotherapy, laser photocoagulation is at least as effective, has less complications, is better tolerated, and is technically easier to administer.[14] No study to date has compared the structural and functional outcomes or time and energy requirements of laser treatment using different modes of a transpupillary diode laser delivery.

Potential advantages of near-continuous mode delivery are increased efficiency due to less need to make power adjustments and improved structural outcomes due to better uptake of laser energy with varying retinal thickness and pigmentation. This may be especially true today with treatment of younger and more premature infants with high-risk prethreshold ROP per the guidelines of the Early Treatment for Retinopathy of Prematurity Trial (ETROP).[15] Visualization of the retina is often more difficult in these infants. The vitreous is hazier and the cornea is often not as clear in these infants. Uptake of laser energy by the retina in this setting is then often more difficult, especially the infants with posterior disease.

Reported direct laser-related complications in high-risk ROP eyes have included cataract, corneal burn, iris burn, retinal, preretinal, or vitreous hemorrhage, choroidal neovascularization, Bruch's membrane rupture, inadvertent photocoagulation of the fovea, preretinal membrane formation, glaucoma, and hypotony.[14,16] Our laser-related complications were infrequent and similar in our two treatment groups. The only serious complication, that of a visually significant cataract, however, occurred in a child treated with pulsed mode therapy. Our structural and functional outcomes were similar in the two treatment groups. These percentages of retinal detachments corresponded to the percentages that occurred in the Cryo-ROP study and in other reported ROP studies that occurred before the ETROP Study. No significant difference existed between the two groups regarding the development of retinal detachment. Although all eyes with macular ectopia belonged to the pulsed mode group, the number of eyes with macular ectopia was too small to yield statistical significance. Strabismus, amblyopia, and myopia, all known to be more frequent in children with retinopathy of prematurity,[6,17-21] were encountered with equal frequency in our two treatment groups.

Near-continuous mode delivery was significantly more time- and energy-efficient than pulsed mode delivery. Treatment time was reduced almost 40%. When both eyes were treated, which is usually the case in ROP, near-continuous treatment had a mean time reduction in our group of 18 minutes. This decrease in time required for the procedure could translate into less anesthetic/sedative medications used and less time on the ventilator, which could then translate into faster time to extubation if the laser procedure is done under general anesthesia. Also, reducing the treatment time could translate into less fatigue for the infant who has the laser procedure done in the neonatal intensive care unit without general anesthesia. This difference in length of anesthesia could be clinically significant in fragile premature infants. Last, near-continuous mode delivery required significantly less total energy. This lower total amount of absorbed energy could potentially lead to fewer laser-related complications, such as hyphema, cataract, iris and corneal burn, and rupture of Bruch's membrane. Our complication rates were low with either modality. The sample size was too small to allow for meaningful statistical comparison of the complications rates.

This study does have some important weaknesses. The first part of the study had with the usual problems of incomplete data for different analyses. The higher follow-up rate in the infants treated with pulsed mode laser introduces potential bias that could interfere with interpretation of the results. The use of several different treating ophthalmologists in the retrospective part of the study, each with a possible preference for one mode of laser application, also could introduce potential bias. There may also be some concern that only nine patients were included in the prospective part of the study. However, the differences between groups were marked, giving a statistical power that was sufficient to show that the observed difference was statistically significant.

In conclusion, we have demonstrated that pulsed mode and near-continuous mode delivery of diode laser photocoagulation for ROP yield similar structural and functional outcomes with no difference in direct laser-related complications during the 6-month period of follow-up. Near-continuous mode delivery, however, in our hands was significantly more time- and energy efficient.

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An Eye on the Arts – The Arts on the Eye

When one thinks of the masses of color and shape in his paintings, perhaps it won't come as a surprise to learn that Cézanne was myopic, although he refused glasses, reputedly crying "Take those vulgar things away!"

—Diane Ackerman (from *A Natural History of the Senses*)