PEDIATRICS

Feb 2000
VOL. 105
NO. 2

Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group*

ABSTRACT. *Objective.* **To determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold retinopathy of prematurity (ROP) to reduce the probability of progression to threshold ROP and the need for peripheral retinal ablation.**

Methods. **Premature infants with confirmed prethreshold ROP in at least 1 eye and median pulse oximetry <94% saturation were randomized to a conventional oxygen arm with pulse oximetry targeted at 89% to 94% saturation or a supplemental arm with pulse oximetry targeted at 96% to 99% saturation, for at least 2 weeks, and until both eyes were at study endpoints. Certified examiners masked to treatment assignment conducted weekly eye examinations until each study eye reached ophthalmic endpoint. An adverse ophthalmic endpoint for an infant was defined as reaching threshold criteria for laser or cryotherapy in at least 1 study eye. A favorable ophthalmic endpoint was regression of the ROP into zone III for at least 2 consecutive weekly examinations or full retinal vascularization. At 3 months after the due date of the infant, ophthalmic findings, pulmonary status, growth, and interim illnesses were again recorded.**

Results. **Six hundred forty-nine infants (325 conventional and 324 supplemental) were enrolled from 30 centers over 5 years. Five hundred ninety-seven (92.0%) infants attained known ophthalmic endpoints, and 600 (92%) completed the ophthalmic 3-month assessment. The rate of progression to threshold in at least 1 eye was 48% in the conventional arm and 41% in the supplemental arm. After adjustment for baseline ROP severity stratum, plus disease, race, and gestational age, the odds ratio (supplemental vs conventional) for progression was .72 (95% confidence interval: .52, 1.01). Final structural status of all study eyes at 3 months of corrected age showed similar rates of severe sequelae in both treatment arms: retinal detachments or folds (4.4% conventional vs 4.1% supplemental), and macular ectopia (3.9% conventional vs 3.9% supplemental). Within the prespecified ROP severity strata, ROP progression rates were lower with supplemental oxygen than with conventional oxygen, but the differences were not statistically significant. A post hoc subgroup analysis of plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) suggested that infants without plus disease may be more responsive to supplemental therapy (46% progression in the conventional arm vs 32% in the supplemental arm) than infants with plus disease (52% progression in conventional vs 57% in supplemental).**

Pneumonia and/or exacerbations of chronic lung disease occurred in more infants in the supplemental arm (8.5% conventional vs 13.2% supplemental). Also, at 50 weeks of postmenstrual age, fewer conventional than supplemental infants remained hospitalized (6.8% vs 12.7%), on oxygen (37.0% vs 46.8%), and on diuretics (24.4% vs 35.8%). Growth and developmental milestones did not differ between the 2 arms.

Conclusions. **Use of supplemental oxygen at pulse oximetry saturations of 96% to 99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery. A subgroup analysis suggested a benefit of supplemental oxygen among infants who have prethreshold ROP without plus disease, but this finding requires additional study. Supplemental oxygen increased the risk of adverse pulmonary events including pneumonia and/or exacerbations of chronic lung disease and the need for oxygen, diuretics, and hospitalization at 3 months of corrected age. Although the relative risk/benefit of supplemental oxygen for each infant must be individually considered, clinicians need no longer be concerned that supplemental oxygen, as used in this study, will exacerbate active prethreshold ROP.** *Pediatrics* **2000;105:295–310;** ***retinopathy of prematurity, oxygen therapy, visual loss, oxygen toxicity, prematurity, neonatal outcomes, bronchopulmonary dysplasia.***

ABBREVIATIONS. ROP, retinopathy of prematurity; CRYO-ROP,

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Received for publication Oct 13, 1999; accepted Nov 2, 1999.
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cryotherapy for ROP; STOP-ROP, Supplemental Therapeutic Oxygen for Prethreshold ROP; PMA, postmenstrual age; SES, socioeconomic status; CLD, chronic lung disease; CPAP, continuous positive airway pressure; OR, odds ratio; CI, confidence interval.

Retinopathy of prematurity (ROP) is a neovascular retinal disorder that develops in 84% of premature survivors born at <28 weeks' gestation. Fortunately, ROP resolves in most cases (80%) without visual loss from retinal detachments or scars.[1,2] The multicenter study of cryotherapy for ROP (CRYO-ROP) study showed that, when the disorder progresses, ablation of the avascular peripheral retina with cryotherapy reduced the incidence of retinal detachment from 51% to 31%.[3] Peripheral retinal ablation, now usually by laser therapy, has become standard treatment for advanced ROP.[4–7] However, this therapy is not always successful in halting the progression of ROP, and the long-term complications of extensive ablation of the developing peripheral retina beyond 5 years of age[7] are as yet unknown.

In 1948, Michaelson[8] proposed that a gradually increasing oxygen deficit of the oxygen-consuming retina during normal differentiation causes release of an angiogenic growth factor. Based on this supposition, therapeutic administration of supplemental oxygen to relieve the putative hypoxic stimulus for retinal neovascularization has been considered. In the 1950s, Szewczyk[9] and Bedrossian et al[10,11] first reported the use of supplemental oxygen to treat the neovascularization in ROP. This approach was abandoned after the 1956 Cooperative Study of Retrolental Fibroplasia demonstrated that prolonged (4 weeks) administration of 50% oxygen caused increased rates of ROP and vision loss.[12] But the concept of an hypoxic stimulus for retinal neovascularization remained biologically plausible and eventually regained scientific interest and attention.

Case–control studies revealed that infants who develop severe ROP, compared with infants of similar gestation and birth weight who do not have ROP, have hospital courses characterized by more complex medical problems, prolonged oxygen requirements, lower overall arterial oxygenation levels, and more episodes of fluctuating blood oxygen levels.[13–15] In contrast to healthy neonates breathing room air, whose arterial oxygen levels are similar to those of adults (95–100 mm Hg [13 pKa]), the recommended arterial concentrations for premature infants receiving oxygen are 50 to 80 mm Hg (6.6–10.6 kPa).[16] This relative hypoxia in premature infants raised the possibility that supplemental oxygen might be used to improve retinal oxygenation and down-regulate retinal neovascularization. Tests of the effects of such oxygen supplementation in animal models of ROP supported this hypothesis,[17,18] and a reported benefit of supplemental oxygen in a clinical case series[19] provided additional support for systematically testing the hypothesis in premature infants with ROP. We report the primary results from the Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) study, which was designed to test the hypothesis that supplemental oxygen, given to attain a pulse oximetry range of 96% to 99% saturation, would reduce by one third the proportion of infants with at least 1 eye progressing from moderate ROP (prethreshold) to threshold ROP requiring peripheral ablative surgery, without unacceptable side effects.[20]

METHODS

Study Design

The study design was a randomized trial comparing the effects of 2 oxygenation strategies on the progression of ROP: conventional oxygenation at a pulse oximetry target of 89% to 94% versus supplemental oxygen to achieve a pulse oximetry target range of 96% to 99%.[21] From February 1994 to March 1999, eligible patients from 30 centers were typically enrolled by telephone call to the central coordinating center (64%) after confirmation of eligibility and signed informed consent by parents or legal guardians. Random assignments were generated by the coordinating center using the Wei-Lachin Urn Scheme[22] and were stratified by center and by 2 levels of baseline ROP severity. When the coordinating center was not available, study centers used sequentially numbered, sealed envelopes provided in advance by the coordinating center to obtain treatment assignments, and submitted appropriate documentation to the coordinating center. An infant was assigned to the severe ROP stratum A whenever either study eye had 1 or more clock hours of any stage ROP in zone I, or when the fellow eye was already at threshold or worse ROP (see Table 1), thereby eliminating that eye as a study eye. The remaining infants fell in the less severe ROP stratum B with zone II prethreshold ROP in both eyes or in the second eye at less than prethreshold ROP. Family, bedside nurses, and attending neonatologists knew the treatment assignment, but the study-certified ophthalmologists who assessed eligibility, progression of the ROP, and study end-

TABLE 1. Definitions of ROP Severity Categories for STOP-ROP

Threshold ROP*	
Zone II	Presence of posterior pole dilation/tortuosity in at least 2 posterior pole quadrants (plus disease), and stage 3 ROP for at least 5 contiguous clock h or 8 composite clock h
Zone I	ROP (any stage) with posterior pole dilation/tortuosity in at least 2 posterior pole quadrants (plus disease), or stage 3 ROP, with or without plus disease
Beyond threshold	Stage 4 ROP, stage 5 ROP, or massive vitreal hemorrhage obscuring the view of the fundus
Prethreshold ROP	
Zone II	Any number of clock hours of stage 3 ROP, less than threshold severity, or any stage 2 ROP with at least 2 quadrants of posterior pole dilation/tortuosity disease (plus disease)
Zone I	Any ROP less than threshold severity

Stages and zones based on the international classification of ROP.[24]

* The definition of threshold ROP differs somewhat from that used in the CRYO-ROP study[4] in 2 ways: 1) In the CRYO-ROP study, "plus disease" was a global assessment of the posterior pole and was not determined according to number of quadrants involved, and 2) in the CRYO-ROP study, the definition of threshold was the same for both zone I and zone II and is the same as stated for zone II above (except for the number of quadrants of posterior pole dilation/tortuosity, as described in note 1). In STOP-ROP, a less stringent definition of threshold in zone I was used to accommodate the clinical judgment of a majority of the participating ophthalmologists that earlier treatment was needed to improve the poor outcomes of zone I threshold ROP.

points remained masked to treatment assignment throughout the study.

The primary endpoint of this study of systemic oxygen therapy was based on the infant, ie, progression of at least 1 study eye of an infant to threshold ROP (Table 1). Infants had only 1 study eye if the fellow eye was already at threshold or worse than threshold ROP at enrollment. Otherwise, they had 2 study eyes; even a fellow eye at less than prethreshold severity was considered a study eye, because it was going to be exposed to the assigned treatment and could progress to threshold ROP. Secondary endpoints included ophthalmic status at 3 months after due date, infant growth rates, developmental screening, and adverse medical events. The protocol was reviewed and approved by the institutional review board at each participating site before initiation of recruitment at that site.

Eligibility Criteria

Premature infants were screened for ROP, according to local guidelines consistent with the 1992 recommendations of the American Academy of Pediatrics,[16] at 71 hospitals affiliated with 30 certified participating centers throughout the United States. Infants with prethreshold ROP in at least 1 eye (Table 1) were registered as potentially eligible for the study and monitored for a minimum of 4 hours with continuous pulse oximetry. Registered candidates were excluded as ineligible whenever their median pulse oximetry was greater than 94% saturation while breathing room air or they had lethal anomalies or congenital anomalies of the eye. The family or guardian of eligible infants was approached for consent if the attending neonatologist agreed that randomization to either oxygen saturation target range could be achieved and would be medically safe, and that the infant's caretaker would be able to comply with the follow-up appointments. The diagnosis of prethreshold ROP in at least 1 eye then had to be confirmed independently by a second examiner to qualify for randomization. At least 1 of the 2 examiners had to be certified by the STOP-ROP study; usually both were.

Intervention

Although randomization and initiation of treatment within 24 hours of the diagnosis of prethreshold ROP was the goal, later enrollment was permitted as long as at least 1 eye was verified as remaining at prethreshold within the preceding 48 hours. The treatment assignment was for the infant to be placed on continuous pulse oximetry monitoring and to maintain oxygen saturation, as much as possible, in the target range of either 89% to 94% (conventional) or 96% to 99% (supplemental). Ohmeda 3740 pulse oximeters and laptop computers with software to monitor, record, and report trends in oxygen saturation were provided by the study for each infant. The Ohmeda 3740 pulse oximeter is calibrated at the factory to display a saturation lower by 1.6 saturation points, compared with other commercial oximeters, to correct for assumed carboxyhemaglobin and methemaglobin levels. Oximeters provided continuous data to a laptop computer that displayed real-time oxygen saturation summary graphs and tables updated every 20 seconds. The percent time in the assigned target range over varying time periods was displayed (Fig 1). Whenever the oxygen saturation was out of the target range for >10 of the previous 20 minutes and the saturation was currently out of range, the computer produced a unique alarm. The alarm limits on the oximeter itself were set according to the each hospital's usual policy. Using this continuous feedback, the bedside nurse or family could readily make necessary adjustments to the oxygen environment to maximize the time spent in the assigned target range. Pulse oximetry values were recorded to a computer disk every 40 seconds during the weeks the infant was on study equipment.

Study saturation targets continued for a minimum of 2 weeks, even if ophthalmic endpoints were reached in both eyes sooner. After those 2 weeks, treatment assignment and equipment were stopped after both eyes reached ophthalmic endpoints. Brief periods off equipment were allowed for procedures or baths. Occasionally an infant was ready for discharge home before reaching study endpoint in both eyes. The parents or guardians were then trained to use the study oximeter and computer to permit the assigned treatment to be continued, recorded, and completed at home.

Outcome Variables

Study-certified ophthalmologists and study center coordinators examined enrolled infants weekly until both eyes reached oph-

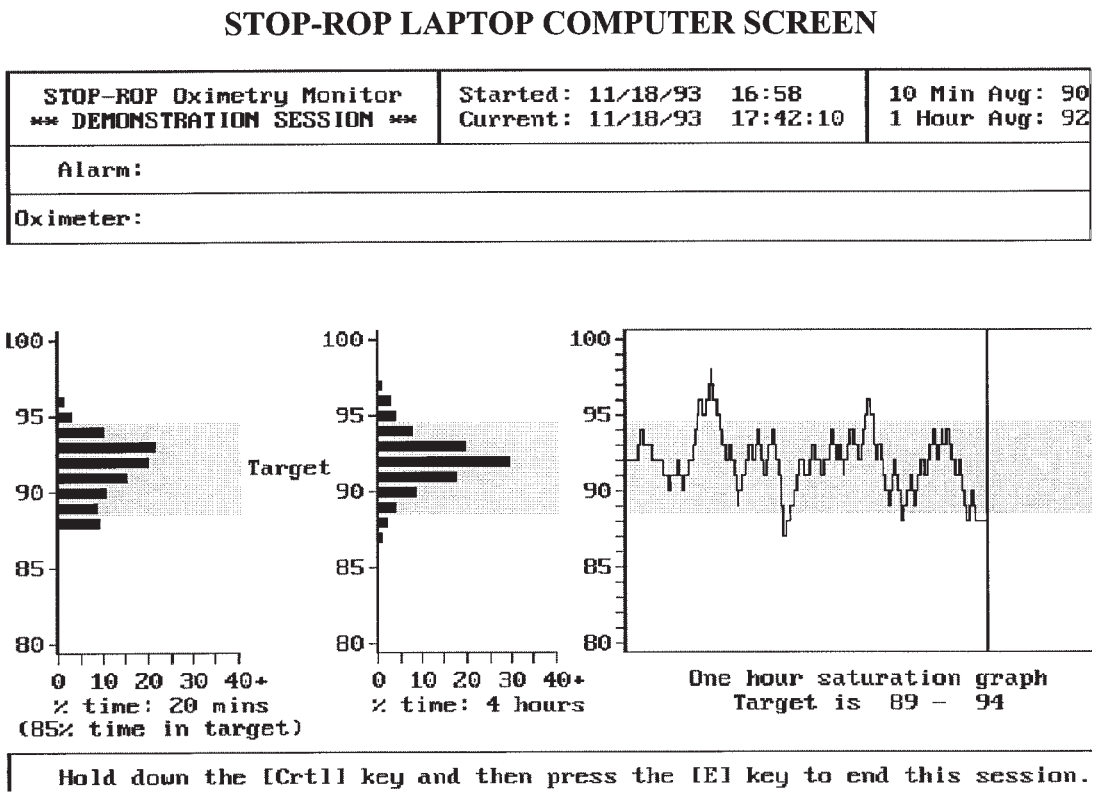


Fig 1. Computer screen format. Frequency distributions and oximetry strip chart information provided continuously at the bedside for nursing management of the pulse oximetry study targets. In this sample, the infant is assigned to the conventional arm (89%–94% saturation), the area highlighted in gray.

thalmic endpoints and again at 3 months' corrected age (that is, 3 months past the term due date of 40 weeks' postmenstrual age [PMA]). The computers and oximeters were covered during examinations to maintain masking of the ophthalmologists. To standardize diagnoses, all ophthalmologists were certified in the completion of study data forms. If they had not been previously certified during the acute phase of the CRYO-ROP or Light Reduction-ROP studies,[23] their use of the international classification of ROP[24] was certified by study headquarters through a series of dual examinations of infants with ROP. Standard fundus photographs of degrees of severity of posterior pole dilation/tortuosity were provided to each center for use at the bedside to promote uniformity of the diagnosis (Fig 2). For the STOP-ROP study, plus disease was defined as "at least 2 quadrants of dilation and tortuosity of the posterior pole vessels." Study personnel completed annual recertification throughout the study.

An adverse ophthalmic endpoint was defined as progression to threshold ROP (or worse), diagnosed by 1 study-certified ophthalmologist and confirmed independently by a second study-certified ophthalmologist. Eyes confirmed to have reached threshold ROP were referred for possible cryotherapy or laser therapy. The definition of threshold ROP (Table 1) in zone II was the same as that used by the CRYO-ROP study; however, in zone I, the definition was modified to permit a diagnosis of threshold at slightly less severity of ROP than required by the CRYO-ROP study because zone I threshold ROP, as defined in CRYO-ROP, progressed to poor retinal outcomes in 78% of eyes even with cryotherapy.[3]

A favorable ophthalmic endpoint was defined as regressing ROP in zone III for at least 2 successive weekly examinations, or full retinal vascularization. Ophthalmic outcomes at 3 months' corrected age were classified as: 1) unfavorable when there were findings of total or partial retinal detachment or when the visual axis was otherwise obstructed, 2) indeterminate when there was macular ectopia, or 3) favorable when there were only minor peripheral findings, laser or cryotherapy scars, or active ROP in zone II or III. The uncommon finding of continued active ROP at 3 months' corrected age was followed whenever possible with a repeat examination at 6 months' corrected age, although this situation had not been anticipated when the STOP-ROP protocol was developed. Whenever missed examinations or death caused incomplete endpoint dating or diagnosis of an eye's endpoint, all available eye data were provided to an ophthalmic endpoints committee of 3 ophthalmologists masked to the treatment assignment. The committee reached consensus on the outcome of each eye according to the following categories: 1) almost certainly reached adverse ophthalmic endpoint, 2) may have reached adverse ophthalmic endpoint, 3) indeterminate, 4) may have reached favorable ophthalmic endpoint, or 5) almost certainly reached favorable ophthalmic endpoint. Only consensus votes of 1 or 5 were used in any subsequent secondary analyses, and the committee was unaware of this analysis decision when they met (votes 2, 3, or 4 were treated as unknown).

Pediatric data were recorded at the time of randomization, at weekly intervals throughout the intervention period, and again at 3 months' corrected age. These data included duration of oxygen use and hospitalization after randomization; weight, length, and head circumference; use of diuretics, methylxanthines, or steroids; a checklist of specified adverse events; and episodes of rehospitalization. The age for achieving full nipple feeds was determined as the first day of 3 consecutive days of taking all enteral feedings by mouth. The questions for the Hollingshead classification of socioeconomic status (SES) were asked at discharge.[25] Adverse events, rehospitalizations, and deaths before 3 months' corrected age were reported as they occurred. The Revised Parental Denver Questionnaire was administered at 3 months' corrected age.[26]

All deaths and rehospitalizations were reviewed by 3 neonatologists masked to treatment assignment to determine whether pulmonary disease was the primary cause of death or rehospital-

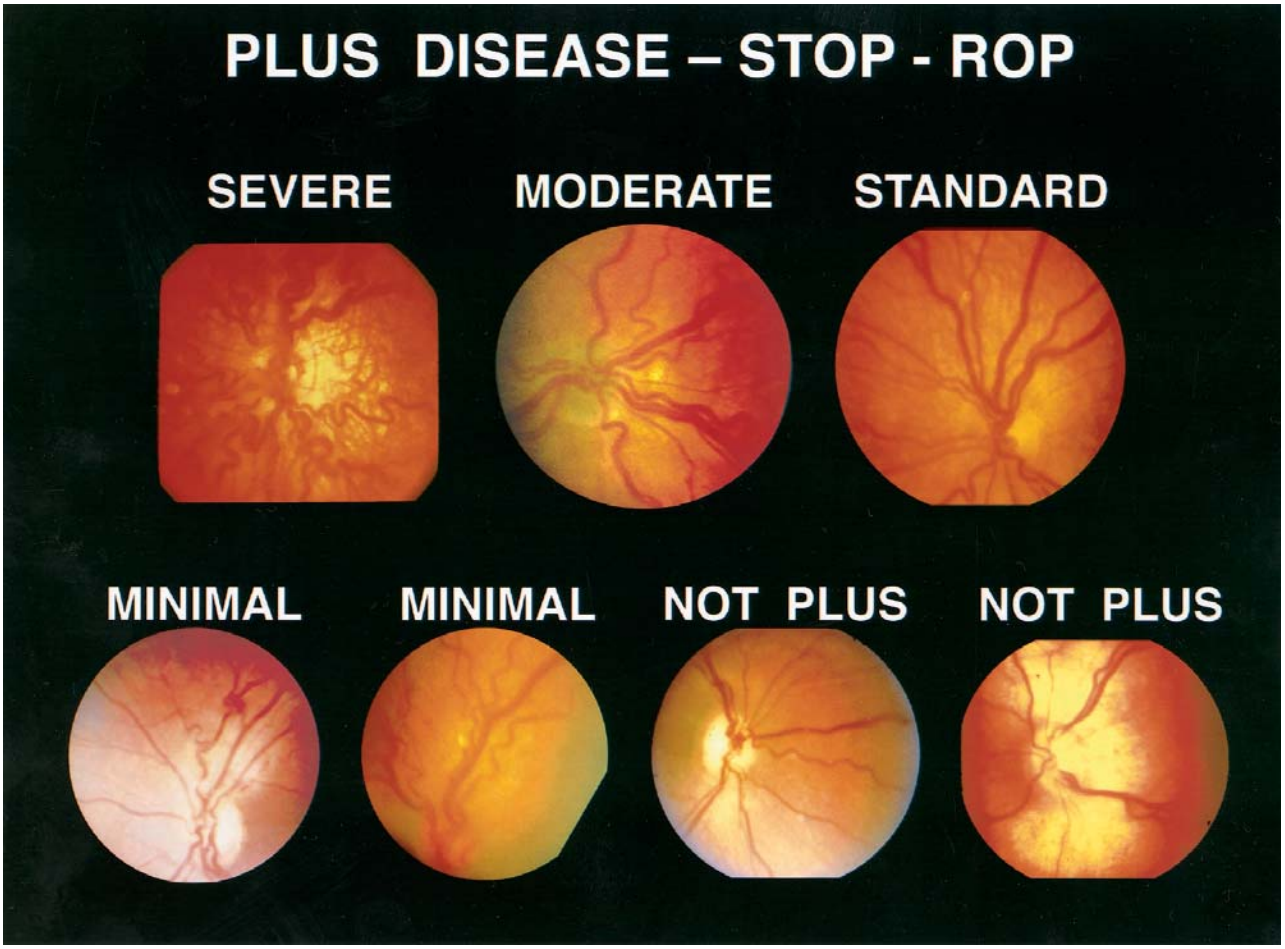


Fig 2. Standard photographs for the STOP-ROP study: fundus photographs of the posterior pole (visible with a direct ophthalmoscope), showing examples of mild to moderate posterior pole dilation/tortuosity and samples of retinas without this finding.

ization. Pneumonia/chronic lung disease (CLD) events were defined as probable or definite pneumonia, an acute exacerbation of CLD, or some combination of these 2 such that the study neonatologist could not distinguish between them.

Pulmonary Score

A composite pulmonary score was developed to describe the pulmonary status of each infant at baseline. The pulmonary score was calculated as:

$$\text{Pulmonary score} = (F_{IO_2})\ (\text{support}) + (\text{medications})$$

where F_{IO_2} is expressed as a fraction (room air = .21); support = 2.5 if on ventilator, 1.5 if on nasal or endotracheal continuous positive airway pressure (CPAP), and 1.0 if on nasal cannula, hood oxygen or off oxygen; and medications = .05 each for methylxanthines or intermittent diuretics, .10 for daily diuretics, .10 for inhaled steroids, and .20 for systemic steroids for CLD. Therefore, the pulmonary score could have a range of values between .21 (no pulmonary support, oxygen, or medications) and 2.85 (assuming that an infant would not be on both inhaled and systemic steroids). The baseline pulmonary score correlated well with pulmonary rehospitalizations, pulmonary deaths, and markers of CLD severity, such as duration of oxygen therapy (data not shown).

Sample Size and Data Monitoring

The progression rate to threshold was monitored by the Data and Safety Monitoring Committee at annual meetings. An early stopping guideline was constructed for ophthalmic benefit at an overall α-value of .025, and a stopping guideline for ophthalmic harm at an overall α-value of .10, allowing for repeated interim analyses[27] using the software of Reboussin (Madison, WI, University of Wisconsin, Department of Statistics). A sample size of 880 infants (to achieve 816 cases with final outcome data) was calculated as necessary to provide 90% power with an overall type I error rate of .025 to detect a one third reduction in progression to threshold disease or a 10% absolute reduction based on a predicted rate of progression of 30% in the conventional arm.[1] Adverse events were reviewed biweekly, and deaths were reviewed immediately by a neonatologist on the Data and Safety Monitoring Committee. All adverse events were reviewed at each meeting of the full Committee.

In 1997, the Data and Safety Monitoring Committee, after the enrollment of 449 children over 3.3 years, expressed concern about the ability of the study group to enroll the target number of 880 infants within 5 years, given consistent enrollment rates averaging 11.2 infants per month. Furthermore, new reports of nonrandomized case series in human infants suggesting a strong beneficial effect of supplemental oxygen,[28,29] as well as publication of additional animal model data,[30–35] supported the hypothesis of the STOP-ROP study, which might adversely affect enrollment. Calculations at that time showed that an enrollment of 633 infants completing the study would provide 83% power to detect a fall in the progression rate from 30% to 20%. The Committee members, who were not masked to study ophthalmic outcomes (although masked to treatment assignment) at the time of the review, recommended that recruitment continue through March 1999 with a revised enrollment goal of at least 633 infants. The final number of 649 enrollees, with ophthalmic endpoints available for 597, resulted in a power of ~80% against the designed alternative.

Statistical Analyses

Primary analyses were performed on all enrollees according to the assigned treatment arm (intention-to-treat) using the group-sequential method of Kim and DeMets.[27] Secondary categorical characteristics of the patients in the 2 arms were compared by χ^2 test, and group differences of continuous factors were compared with Student's t test and Wilcoxon rank-sum test. Logistic regression was used for the adjustment of progression rates for covariates. All P values presented are 2-sided and are unadjusted for the 5 interim examinations of the data, ie, are nominal P values, unless otherwise specified. Analyses were conducted with SAS software (SAS Institute, Cary, NC).[36]

RESULTS

Patients

Comparability of Enrolled and Registry Infants

From February 9, 1994, through March 31, 1999, 1847 infants with prethreshold ROP in at least 1 eye were registered at the participating centers. Of these, 634 (34%) were ineligible because either their pulse oximetry was greater than 94% in room air, or they had fatal or congenital eye anomalies (Fig 3). Of 1213 clinically eligible infants, 649 (54%) were enrolled. Reasons for nonenrollment were refusals of the family/guardians or the neonatologist (368), nonconfirmed prethreshold ROP (41), enrollment in conflicting studies (9), judgment that the infant was too ill to attempt randomization to the supplemental arm (28), inability of the family to comply with follow-up visits (41), imminent transfer to another hospital (8), and others. Of the ineligible infants, 99% had pulse oximetry greater than 94% in room air. Nonenrolled infants, including both those ineligible and those eligible but not enrolled (1198), weighed more at birth than enrolled infants (787 ± 287 vs 726 ± 160 g; $P < .001$) and had a slightly higher gestation at birth (25.7 ± 1.8 vs 25.4 ± 1.5 weeks; $P < .01$).

Comparability of Treatment Arms

Of the enrolled infants, 325 were randomized to the conventional arm, 324 to the supplemental arm, and their study completion rates are shown in Fig 3. The primary ophthalmic endpoint was available for 597 (92%) and was not recorded for 52 infants because of death (2), parental withdrawals from the study treatment (18), treatment with cryotherapy/laser before reaching ophthalmic endpoints (5), and missed eye examinations (27). Ophthalmic evaluations at 3 months' corrected age were completed for 600 infants and were unavailable for 49 because of death (16), withdrawal (31), and loss to follow-up (2). (Three additional infants in the supplemental arm not shown in the figure returned for just the neonatal portion of the 3-month evaluation). Rates of noncompletion were similar for both treatment arms (Fig 3).

Baseline demographic and pediatric characteristics are shown in Table 2, and ophthalmic baseline characteristics in Table 3. Randomization resulted in similar groups. Enrollment and randomization occurred at a PMA (PMA = gestational age at birth plus chronological age) of 35.4 ± 2.5 weeks (range: 30–48 weeks). The baseline pulmonary severity score and the mode of oxygen support were similar between the 2 arms. Many infants were on diuretics (54%) and methylxanthines (70%), and 29% had received steroids for CLD in the week before enrollment.

The ophthalmic baseline characteristics shown in Table 3 were also similar between the conventional and supplemental arms. There were no significant differences between the treatment arms in the number of infants enrolled in each ROP severity stratum or substratum. For the more severe forms of ROP represented in stratum A, 4.3% of enrollees had 1 eye at or beyond threshold (therefore, only 1 study eye), and 23.4% had 1 or both eyes with at least 1 clock hour of ROP in zone I. In stratum B, infants with

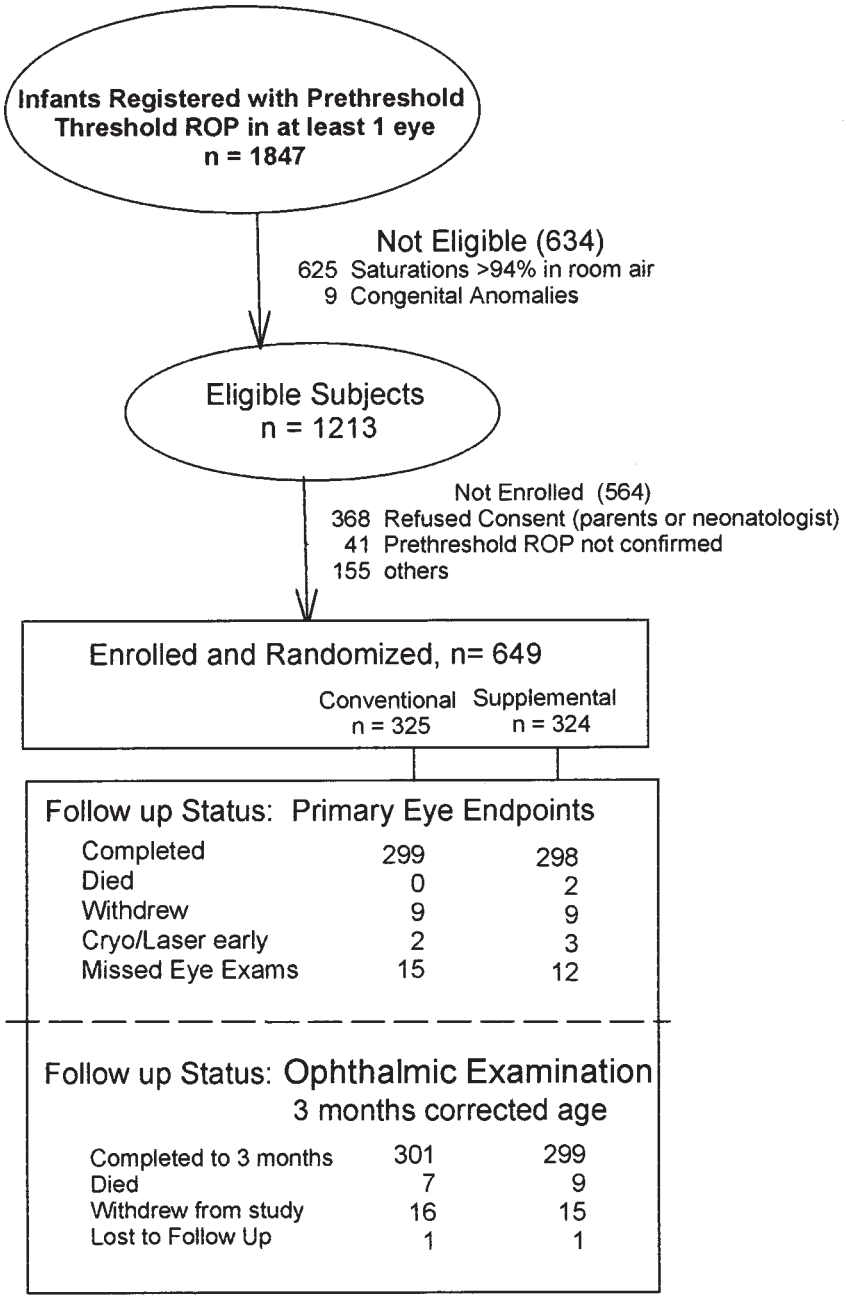


Fig 3. Patient enrollment flow diagram. There were several subjects without primary ophthalmic endpoints who nonetheless continued with follow-up examinations; therefore, there are more completed 3-month examinations than primary ophthalmic endpoints. Three additional supplemental infants completed the 3-month neonatal outcome examination, although they failed to complete the ophthalmic 3-month examination (not shown in figure).

zone II ROP in both eyes comprised 51% of all enrollees, and the remaining 21% entered the trial with the prethreshold eye's fellow eye at less than prethreshold ROP. There were no significant differences between the 2 arms in the number randomized within the first 24 hours after observing prethreshold ROP and in the numbers randomized after a longer period (Table 3). The elapsed time from the first diagnosis of prethreshold ROP to randomization was <24 hours in 33% of infants and >48 hours in 27% of infants.

Adherence to the Protocol

Oxygen requirements increased significantly for the infants randomized to the supplemental range. The average oxygen concentration increased from 36% ± 14% pretreatment to 46% ± 20%, 24 hours after randomization for those infants on a ventilator, CPAP, or hood oxygen; the average increase was 9.5% ± 16.5%. For infants on nasal cannula, the interactions between flow, infant size, and the oxygen concentration administered by cannula made estimation of the change in oxygen concentration more complex. Using the conversion formula of Benaron and Benitz,[37] average transformed oxygen concentration for infants on nasal cannula rose from 26% ± 6% before, to 31% ± 11% 24 hours after randomization to the supplemental arm; the average increase was 5% ± 9%. During the same 24-hour period, infants assigned to the conventional arm experienced a change from 36% ± 17% to 32% ± 15% in the infants on a ventilator, CPAP, or hood oxygen, and from 28% ± 10% to 26% ± 11% in the nasal cannula infants. (The 53 conventional and 25 supplemental

TABLE 2. Baseline Characteristics of Enrollees

	Number Enrolled		
	Conventional 325	Supplemental 324	Totals 649
Birth weight (g)*	721 ± 160	731 ± 161	726 ± 160
Gestational age (wk)*	25.4 ± 1.5	25.4 ± 1.5	25.4 ± 1.5
PMA (wk)*	35.3 ± 2.6	35.4 ± 2.5	35.4 ± 2.5
Weight at entry (g)*	1538 ± 445	1556 ± 442	1547 ± 443
Gender (% male)	53.9%	60.5%	57.2%
Race			
White	180 (55%)	179 (55%)	359 (55%)
Black	91 (28%)	101 (31%)	192 (30%)
Hispanic	31 (10%)	26 (8%)	57 (9%)
Others	23 (7%)	18 (6%)	41 (6%)
Pulmonary status			
Pulmonary score*	.53 ± .36	.56 ± .37	.55 ± .37
Ventilator	46 (14%)	57 (18%)	103 (16%)
CPAP or hood	57 (18%)	55 (17%)	112 (17%)
Nasal cannula	210 (64%)	203 (63%)	413 (64%)
No oxygen	12 (4%)	9 (3%)	21 (3%)
Medications			
Methylxanthines	68.6%	72.5%	70.1%
Diuretics	52.3%	57.1%	54.1%
CLD steroids†	28.1%	30.6%	29.3%
SES‡			
High (35–66)	27%	27%	27%
Intermediate (20–34)	30%	29%	29%
Low (0–19)	29%	26%	27%
Missing	14%	19%	16%

* Mean ± standard deviation.
† Steroids given systemically for CLD within the past week, not including inhaled steroids. Excludes 33 conventional and 40 supplemental infants from the early months of the study when data on the use of steroids were not being collected.
‡ SES by Hollingshead criteria,[25] as assessed at discharge.

TABLE 3. Baseline Ophthalmic Characteristics By Treatment Group

Characteristic	Conventional		Supplemental		Total	
	n	%	*n*	%	*n*	%
	325	100%	324	100%	649	100%
Stratum A—at least 1 eye PT ROP*						
Fellow eye worse than PT	14	4.3%	14	4.3%	28	4.3%
At least 1 eye zone I†	77	23.7%	75	23.2%	152	23.4%
Stratum B—at least 1 eye PT						
Both eyes zone II PT	167	51.4%	164	50.6%	331	51.0%
1 eye less than PT	67	20.6%	71	21.9%	138	21.3%
Infants with zone I ROP	88	27.1%	91	28.1%	179	27.6%
Infants with zone II ROP	237	72.9%	233	71.9%	470	72.4%
Plus disease infants‡	107	32.9%	112	34.6%	219	33.7%
Non-plus disease infants	218	67.1%	212	65.4%	430	66.3%
Time from first§ PT diagnosis to randomization (infants in category)						
≤24 h	115	35.5%	100	31.6%	215	33.2%
>24, ≤48 h	127	39.2%	128	39.6%	255	39.4%
>48 h	82	25.3%	95	29.4%	177	27.4%
Missing	1		1		2	

* PT indicates prethreshold retinopathy of prematurity.
† Note that in stratum A, infants with bilateral zone I ROP and 1 eye already at threshold or beyond, are categorized as "fellow eye worse than prethreshold."
‡ Plus disease is defined as present when there is posterior pole vascular dilation and tortuosity in at least 2 quadrants. An infant is a plus disease infant if at least 1 study eye has plus disease at baseline. Similarly, an infant is a zone I infant if at least 1 study eye has zone I ROP.
§ "First PT diagnosis" is the date/time of the first examination that showed prethreshold ROP in at least 1 eye that was subsequently confirmed on a second examination.

infants who changed mode of support in 1 direction or the other between nasal cannula and ventilator/CPAP/hood during the first 24 hours after randomization are not included in these calculations.)

Table 4 demonstrates that the distributions of median saturations achieved over the first 2 weeks after randomization were different for the 2 treatment arms. During the first 2 weeks, only 8.0% of median saturations for infants assigned to the conventional arm were in the supplemental range or higher, and

TABLE 4. Distribution of Infants According to Median Pulse Oximetry Over the First Two Weeks on Study

Median Pulse Oximetry Value Over First 2 Weeks, (%)	Conventional Arm* $n = 325$	Supplemental Arm* $n = 324$
<89	.0	.0
89	.0 |	.0
90	.3 |	.0
91	16.9 |	.0
92	34.5 |	.3
93	19.1 |	.3
94	14.5 |	1.2
95	6.2	6.8
96	3.7	23.5 |
97	2.8	56.5 |
98	.9	9.6 |
99	.0	.6 |
100	.6	.3
Missing	.6	.9

The | symbols indicate the targeted range of saturation values for each arm of the study.
* Each study arm column gives the percentage of all subjects in that column whose median pulse oximetry over the first 2 weeks on study was at the level shown in the left hand column.

only 1.8% of median saturations of infants assigned to supplemental therapy were in the conventional range or lower. Pulse oximetry was recorded from all enrollees for these first 2 weeks of study participation, but beyond this period, as the eyes reached study endpoints, fewer infants remained on equipment to contribute to the accumulating oximetry data. In addition, as some infants in the conventional arm had resolution of their CLD, their saturations became greater than 95% while breathing room air. Figure 4 shows the smoothed overall frequency distribution of the saturation values (1 reading every 40 seconds) for the full period until ophthalmic endpoints for all infants enrolled. These data also include the 81 conventional and 85 supplemental infants who continued to use study equipment at home. Refusal of the parents or guardians to take the study equipment home on the day of discharge was a primary cause of premature cessation of pulse oximetry and study assigned oxygenation, occurring in 26 conventional and 24 supplemental subjects. Many of these families/guardians were willing to continue returning for weekly follow-up examinations, and therefore, were not withdrawn from the study. Comparison of the SES of families who refused equipment, with those that accepted it at home, showed no relationship between SES and refusal of this major home challenge, nor success in remaining in the target zones at home (data not shown).

Ophthalmic Outcome Data

The primary outcome, the proportion of infants with at least 1 eye progressing to confirmed threshold ROP, is shown by treatment arm in Table 5 for all infants and for subgroups of infants defined by baseline ophthalmic characteristics. Overall, 48.5% (145/299) of infants with study endpoints and assigned to the conventional arm progressed to confirmed threshold ROP in at least 1 eye, compared with 40.9%

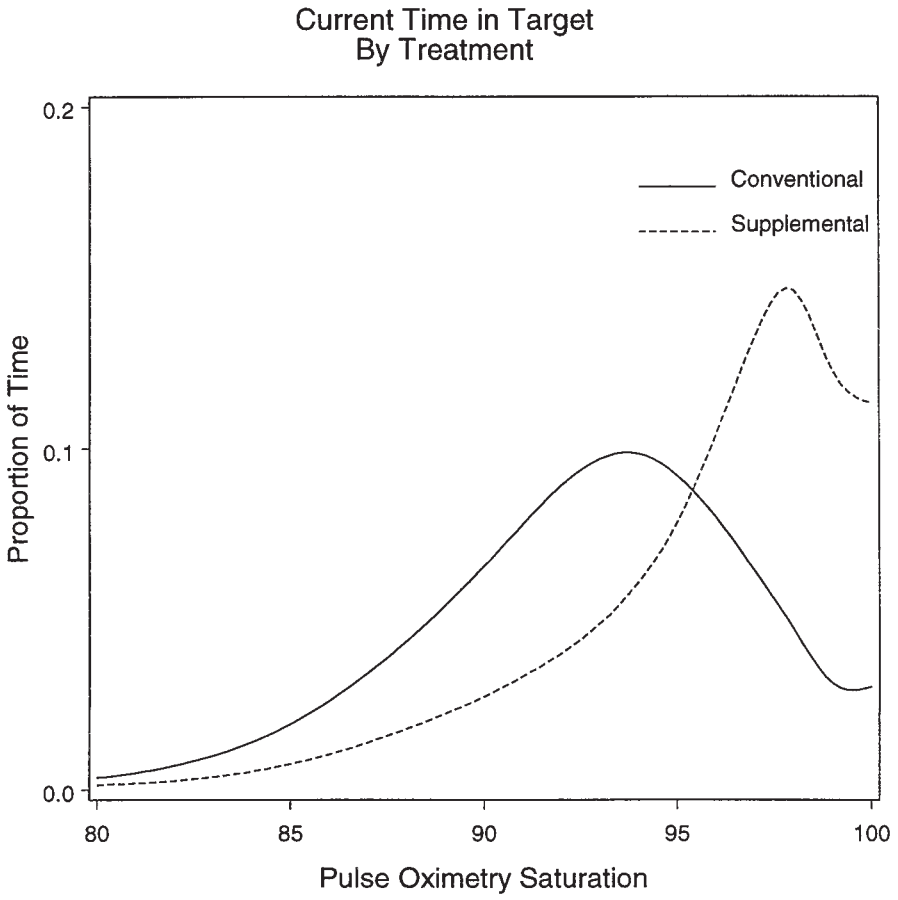


Fig 4. Smoothed frequency distribution of pulse oximetry saturation values for the conventional and supplemental oxygen arms throughout the duration of time on study equipment. Pulse oximetry saturation values were recorded to disk for later analysis once every 40 seconds throughout the time an infant remained on study equipment (range: 2–25 weeks).

TABLE 5. Progression to Threshold ROP* by Ophthalmic Characteristics and Treatment Assignment

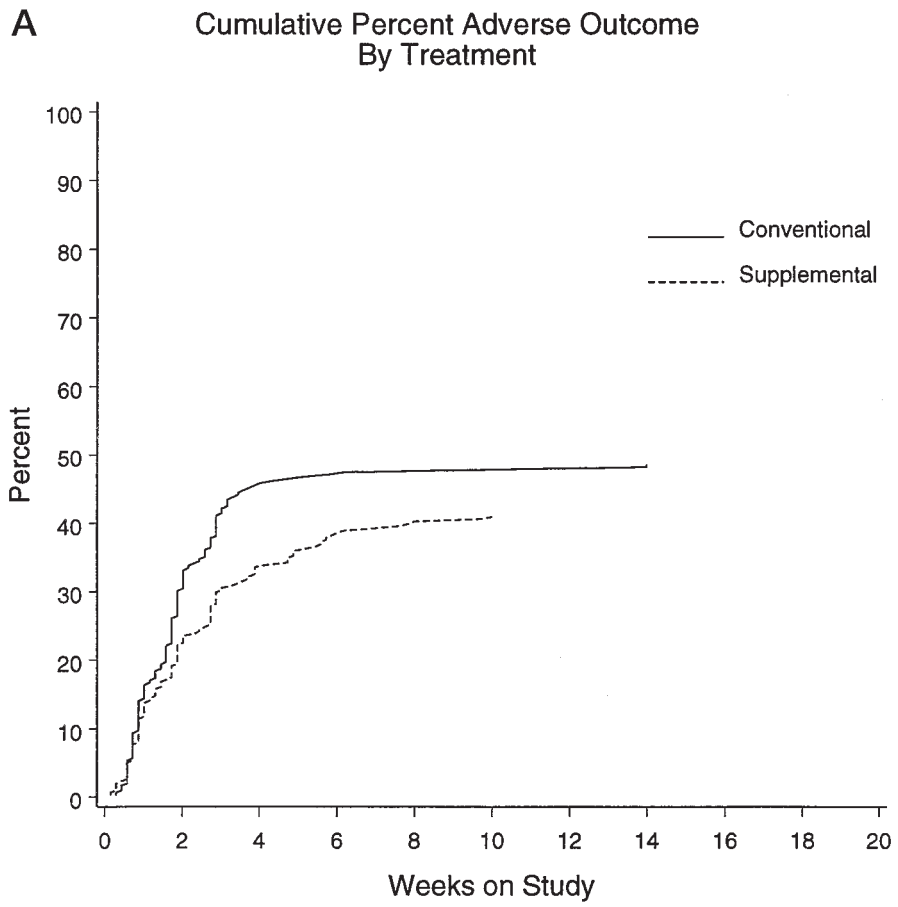
Characteristic	Conventional		Supplemental		Total	
	n	%	*n*	%	*n*	%
Enrolled	325	100%	324	100%	649	100%
Without eye endpoints†	26	8%	26	8%	52	8%
With eye endpoints†	299	92%	298	92%	597	92%
Infants with eye endpoints†	299	100%	298	100%	597	100%
Progression to threshold	145	48%	122	41%	267	45%
Stratum A (progressed/total)	46/84	55%	37/81	46%	83/165	50%
Fellow eye worse than PT‡	8/13	62%	8/14	57%	16/27	59%
At least 1 study eye zone I	38/71	54%	29/67	43%	67/138	49%
Stratum B (progressed/total)	99/215	46%	85/217	39%	184/432	43%
Both eyes zone II PT	80/152	53%	66/152	43%	146/304	48%
1 eye less than PT	19/63	30%	19/65	29%	38/128	30%
Infants with zone I ROP, in at least 1 eye	46/82	56%	41/83	49%	87/165	53%
Infants with zone II ROP	99/217	46%	81/215	37%	180/432	42%
Plus disease infants§	54/103	52%	59/103	57%	113/206	55%
Non-plus disease infants§	91/196	46%	63/195	32%	154/391	39%
Time elapsed from randomization‖						
All study eyes						
To adverse outcome, wk	2.4 ± 2.0		2.7 ± 2.0		2.5 ± 2.0	
To favorable if resolved, wk	9.0 ± 3.8		9.5 ± 4.0		9.2 ± 3.9	
Eyes <PT ROP at randomization	14/62 (22.6%)		14/61 (23.0%)		28/123 (22.8%)	
To adverse outcome, wk	1.7 ± 1.1		3.2 ± 1.3		2.4 ± 1.4	
To favorable outcome, wk	7.8 ± 3.8		8.2 ± 3.9		8.0 ± 3.8	
Eyes without plus disease						
To adverse outcome, wk	2.3 ± 2.1		2.7 ± 2.0		2.5 ± 2.1	
To favorable outcome, wk	8.9 ± 4.0		9.5 ± 4.1		9.2 ± 4.1	
Eyes with plus disease						
To adverse outcome, wk	1.6 ± 1.0		2.2 ± 1.9		1.9 ± 1.6	
To favorable outcome, wk	7.5 ± 2.9		7.1 ± 3.3		7.3 ± 3.1	

* Infant ophthalmic outcomes based on progression of at least 1 study eye to threshold ROP. If an infant entered the study with 1 eye already at threshold or worse, that eye was not a study eye, and the infant's outcome is based on only the study eye.
† "Eye endpoints" means that for that infant, the primary endpoint of either 1) at least 1 eye progressing to threshold, or 2) all study eyes not progressing to threshold is known.
‡ PT indicates prethreshold ROP.
§ "Plus disease infants" are those who have at least 2 quadrants of posterior pole dilation/tortuosity in at least 1 study eye, whereas "non-plus disease infants" have all study eyes with 0 or 1 quadrant of posterior pole dilation/tortuosity.
‖ Mean ± standard deviation.

(122/298) in the supplemental arm. The difference between treatment arms was not significant at the designed 1-tailed α-level of .025, as adjusted for sequential testing. However, the difference was still suggestive, with a 1-tailed P value adjusted for repeated interim analyses of .032.[38] When eyes whose outcomes could be assigned by the Ophthalmic Endpoints Committee were included (31 infants: 15 conventional and 16 supplemental), the progression rates remained similar: 46.2% (145/314) and 39.5% (124/314) for the conventional and supplemental arms, respectively (data not shown).

Analysis by stratum or zone of baseline ROP yielded similar results. The high severity ROP stratum A infants progressed to threshold more frequently than the lower risk stratum B infants (50% vs 43% overall). Higher rates of progression in the conventional arm than in the supplemental arm were observed for both ROP severity strata (55%–46% in stratum A and from 46%–39% in stratum B). When severity was alternatively examined by zone of prethreshold ROP, progression rates also were lower in the supplemental arm (56% vs 49% for zone I and 46% vs 37% for zone II; conventional vs supplemental, respectively); however, none of these differences were statistically significant. In contrast, when progression rates were examined in relation to plus disease, the subgroup analysis revealed a difference. Infants without plus disease in either study eye progressed to threshold 46% versus 32% of the time in the conventional and supplemental arms, respectively ($P = .004$). When at least 2 quadrants of posterior pole dilation/tortuosity were present in either study eye at baseline, 52% of conventional versus 57% of supplemental infants had at least 1 eye progress to threshold ($P = .484$).

Adverse outcomes occurred soon after randomization in both groups as shown in Fig 5A, and the elapsed time from study entry to adverse ophthalmic endpoints was slightly longer in the supplemental arm compared with the conventional arm. Mean progression time to threshold disease was 2.4 weeks for eyes in the conventional arm and 2.7 weeks for eyes in the supplemental arm. Eyes with plus disease at study entry progressed to threshold disease most rapidly, at a mean of 1.6 and 2.2 weeks in the conventional arm and supplemental arm, respectively. Eyes without plus disease took somewhat longer (mean of 2.3 weeks and 2.7 weeks, respectively; Table 5). Achieving a favorable outcome took longer (Fig 5B), and the time to full vascularization or zone III vessels on 2 consecutive examinations in eyes



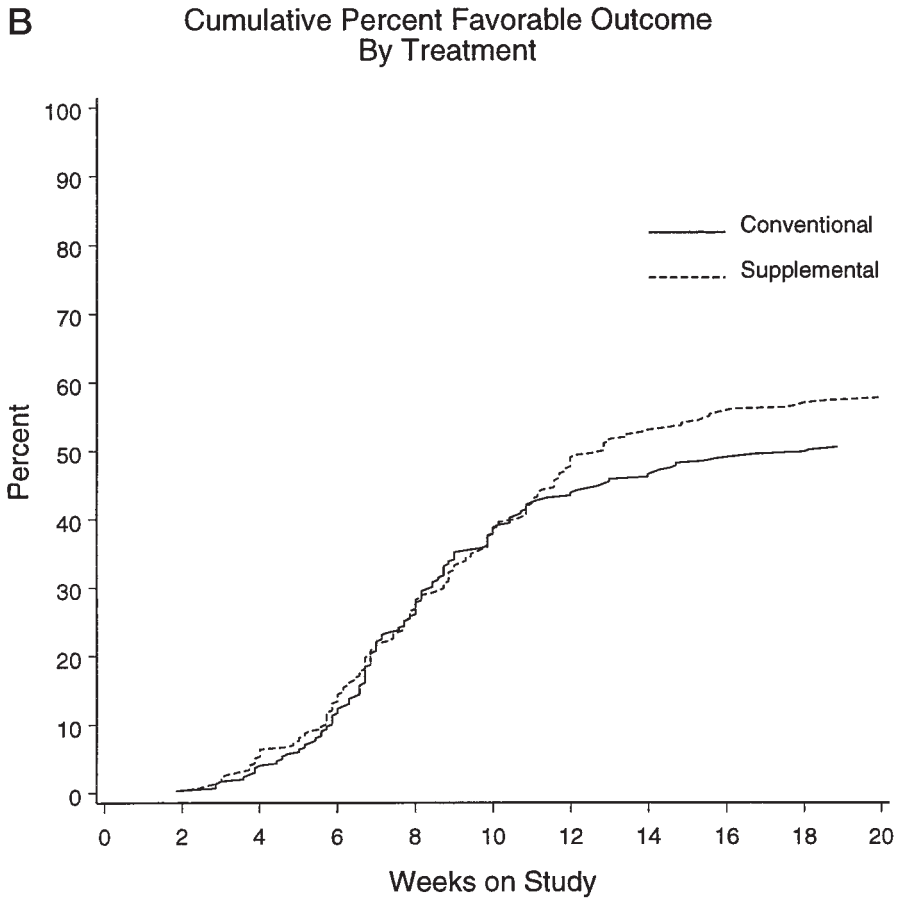


Fig 5. Cumulative rate curves demonstrating the differences in both the proportion and timing of adverse (A) and favorable (B) ophthalmic outcomes by study arm.

without progression to threshold disease occurred in the conventional arm at a mean of 9.0 weeks and in the supplemental arm at a mean of 9.5 weeks. Threshold ROP, when it occurred, was diagnosed at an average PMA of 36.8 weeks (range: 31.6–50.9 weeks) in the conventional arm, and an average of 37.3 weeks' PMA (range: 32.3–45.1 weeks) in the supplemental arm (data not shown in table).

Multiple regression analysis was conducted to adjust for minor variations in baseline characteristics with both simple and complex models. The complex model included treatment assignment, ROP stratum, race, gender, gestational age, small for gestational age status, the baseline pulmonary severity score, plus disease, late versus on-time enrollment, degree of compliance with assigned saturations, interactions of these variables with treatment assignment, and study center. The analysis did not alter the conclusions, but did confirm that both black race (odds ratio [OR]: .44; 95% confidence interval [CI]: .20,.94) and higher gestational age (OR: .80 per week; 95% CI: .66,.98) provide important significant protective effects in reducing the chance of progression of prethreshold ROP to threshold ROP, regardless of treatment arm, while having 2 or more quadrants of posterior pole dilation/tortuosity (plus disease) increased the risk of progression to threshold (OR: 1.71; 95% CI: .95,3.10). In the simplified model, the OR for the supplemental arm after adjustment for ROP risk stratum, plus disease, race, and gestational age was .72 (95% CI: .52,1.01).

Peripheral ablation utilized laser therapy in 93% of treated eyes (73% diode and 20% Argon) and cryotherapy alone in 7%. Four percent of treated eyes received both laser and cryotherapy. Final ophthalmic outcomes based on all study eyes at 3 months' corrected age (or 6 months for 12 conventional and 18 supplemental eyes) revealed adverse outcomes (partial or total retinal detachment, retinal folds, or obstruction of the visual axis) in 4.4% of the study eyes in the conventional and 4.1% in the supplemental arms, and macular ectopia in an additional 3.9% of the study eyes of the conventional arm and 3.9% of the study eyes of the supplemental arm. Among just those eyes that developed threshold ROP and were treated with peripheral surgical ablation, 9.2% in the conventional arm and 13.2% in the supplemental arm had adverse ophthalmic outcomes at 3 to 6 months (excludes macular ectopia that occurred in 6.3% of conventional and 7.7% of supplemental laser/cyro-treated eyes).

Pediatric Outcomes

We hypothesized that infants in the supplemental arm would grow and gain weight faster than infants in the conventional arm, but there were no differences between their growth rates during the initial first 2 weeks, later during the hospitalization period (data not shown), or at 3 months' corrected age (Table 6).

However, markers of CLD severity both during hospitalization and remaining at 3 months' corrected age (50 weeks' PMA) suggest a somewhat worse pulmonary status in the supplemental arm after randomization, although there were no differences in the baseline status measures (Table 2). As shown in Table 6, the conventional arm had fewer infants with 1 or more episodes of pneumonia or CLD exacerbation than did the supplemental arm, 25 (8.5%) versus 38 (13.2%; $P = .066$), and there were also fewer total episodes in the conventional arm (29 vs 51). Using the baseline pulmonary scores to further examine this, infants were divided into higher and lower pulmonary risks at the overall median pulmonary score of .430. The difference in pneumonia/CLD events was confined to the infants with the higher half of the pulmonary scores (10.6% in the conventional arm vs 18.7% in the supplemental arm; $P = .051$) and did not differ among the infants with the lower half of the pulmonary scores (6.5% in the conventional arm vs 6.8% in the supplemental arm; $P = .93$; data not in table). Rehospitalization rates for pulmonary causes (excluding for apnea alone), and death rates from pulmonary causes were similar in the 2 arms (Table 6). However, at the 3-month examination (50 weeks' PMA), more infants in the supplemental arm remained hospitalized (12.7% vs 6.8%; $P = .012$), on oxygen (46.8% vs 37.0%; $P = .020$), and on diuretics (35.8% vs 24.4%; $P = .002$). The proportion of infants who experienced any 1 or more of these adverse pulmonary events by 3 months' corrected age as defined by remaining hospitalized, remaining on study equipment, oxygen, steroids, methylxanthines, or diuretics was significantly higher in the supplemental arm than in the conventional arm (57% vs 46%, respectively; $P = .005$). Regression analysis adjusting for the important baseline covariates of race, ROP severity, gestational age, and pulmonary status did not change the significance of these findings.

Adverse events from sepsis without pneumonia did not differ between the 2 arms, and survival through the 3-month examination was similar (97.8% conventional vs 97.2% supplemental). Mean PMA at discharge for those infants going home was the same in both arms at 41 ± 3 weeks (range: 35–56), and infants in both arms were able to take oral feeds without a gastric tube at the mean PMA of 39 weeks. At the 3-month follow-up examination, developmental levels as assessed by the Revised Parental Denver Questionnaire were similar (equivalent ages = 3.5 ± 1.4 months in the conventional arm vs 3.4 ± 1.4 months in the supplemental arm).

DISCUSSION

These findings demonstrate that supplemental oxygen, as used in this study for prethreshold ROP, did not significantly decrease the proportion of infants who have at least 1 eye progress to threshold ROP, although the differences were close to nominal statistical significance. Using the observed conventional progression rate of 48%, the study has a power of 70% against a 10-percentage point absolute difference, and a power of 98% against a one third reduction, adjusting for the use of repeated interim analyses as described above. The resultant power is lower than expected because the adverse ophthalmic outcome rate in the conventional group was higher than expected.

TABLE 6. Pediatric Outcomes Between Randomization and Three Months' Corrected Age*

	Conventional $n = 325$	Supplemental $n = 324$
Event occurring after randomization		
Weight gain over the first 2 wk (g; mean ± standard deviation)	291 ± 137	278 ± 143
Length gain over the first 2 wk (cm; mean ± standard deviation)	1.8 ± 1.8	1.7 ± 2.0
Head circumference increase the 1st 2 wk (cm; mean ± standard deviation)	1.6 ± 1.0	1.4 ± .9
PMA at discharge home† (wk; mean ± standard deviation)	41.1 ± 3.3	41.3 ± 3.4
PMA to achieve oral feeding‡ (wk; mean ± standard deviation)	39.0 ± 3.5	38.9 ± 3.6
Infants with pneumonia/CLD events (total # of events)§	25 (29)	38 (51)
Infants with sepsis, but no pneumonia/CLD (total # events)	12 (12)	11 (11)
Infants with apnea/bradys triple baseline (total # events)	26 (36)	30 (33)
Outcomes at the 3-month corrected age window‖		
Remained hospitalized¶ (%)	6.8%	12.7%
Remained on study equipment (%)	3.1%	3.4%
Remained on oxygen (%)	37.3%	46.8%
Remained on steroids (%)	12.5%	14.2%
Remained on methylxanthines (%)	13.5%	14.7%
Remained on diuretics (%)	24.4%	35.8%
Infants with any 1 of the above, # of infants (%)#	148 (45.5%)	183 (56.5%)
Outcomes at 3 months' corrected age examination	$n = 301$	$n = 302$
Infants rehospitalized (# of all rehospitalizations)	99 (132)	87 (116)
Infants rehospitalized for pulmonary reasons, not apnea (# of all rehospitalizations)	46 (53)	41 (49)
All deaths, *n* (pulmonary cause of death, *n*)	7 (3)	9 (5)
Room air saturations too low to test, *n* (%)	17 (6%)	35 (12%)
Room air oxygen saturation for those tested, mean ± standard deviation	95.3 ± 4.7%	94.6 ± 7.7%
Weight gain from randomization (mean ± standard deviation; kg)	2.96 ± 1.00	2.88 ± 1.05
R-PDQ developmental level** (mean ± standard deviation; mo)	3.5 ± 1.4	3.4 ± 1.4

* Corrected age indicates months after the date an infant should have been born at full term (3 months' corrected = 52 weeks' PMA).
† Limited to infants who were discharged to home (ie, excludes deaths, loss to follow-up, and those remaining hospitalized at the 3-month examination).
‡ Excludes 16 conventional and 33 supplemental infants who were not yet feeding by mouth by 50 weeks' PMA, 2 conventional and 7 supplemental infants who died before oral feeds, and 6 conventional and 7 supplemental infants with incomplete data. Oral feeds means that the infant was taking all enteral feedings by nipple (bottle or breast).
§ Excludes 30 conventional and 36 supplemental infants recruited early in the trial for whom these data were not collected.
‖ The 3-month corrected age window was a target of 12 ± 2 weeks after due date, or 50 to 54 weeks' PMA. Outcomes are reported as of 50 weeks' PMA to permit comparisons as some infants were examined late in the window or outside this window.
¶ Values exclude 31 infants with missing data at 50 weeks' PMA attributable to loss to follow-up (14 conventional and 17 supplemental).
# Number of infants, and percent of all enrollees represented by any 1 or more of the 3-month events.
** R-PDQ indicates the Revised Parental Denver Questionnaire.[26]

In STOP-ROP, the observed rate of progression from prethreshold to threshold (48%) in the conventional arm is higher than reported in the CRYO-ROP study (33%) for a number of reasons that can be identified. The eligibility criteria for STOP-ROP excluded nearly half of the infants who would have been included in the CRYO-ROP study, and these were the ones that did not require oxygen and had less severe lung disease at the time of prethreshold ROP. The STOP-ROP enrollees had lower birth weights than the CRYO-ROP infants (726 g in STOP-ROP vs ~850 g for CRYO-ROP prethreshold).[1] During the CRYO-ROP study, borderline threshold cases were judged as not threshold, to avoid treating eyes with an unproven intervention. Because peripheral ablation has been demonstrated to be effective for threshold ROP, this is no longer true, and as in clinical practice, the STOP-ROP study judged in favor of the diagnosis of threshold disease in borderline cases. Finally, the differences in the STOP-ROP definition of threshold ROP in zone I (see Table 1) would result in more infants being diagnosed with threshold ROP during the STOP-ROP trial.

The STOP-ROP results differ from the 2 smaller case series in the literature in which supplemental oxygen for infants with prethreshold ROP was associated with a high regression rate of prethreshold ROP without the need for ablative retinal surgery.[28,29] Some of the possible explanations are differences in patient selection, level of oxygen administration, timing of the intervention, and use of historical controls in the case series. Infants in these case series may have had milder ROP than those enrolled in STOP-ROP, and the effect of that would be higher progression rates in STOP-ROP. The average birth weight of the infants in that series was 814 g, heavier than the 726-g average birth weight of infants enrolled in STOP-ROP, and therefore, at lower risk for severe ROP. In the Gaynon et al[28] series, if infants were mostly detected as having pretheshold ROP before developing plus disease, the findings in that series and the subgroup of infants in STOP-ROP without plus disease would be more consistent. Large differences in reported improvements between historically controlled case series and randomized trials are well recognized and are usually attributed to changes in several aspects of medical care over time, as well as patient selection. STOP-ROP expended considerable effort to maximize the time infants were in their targeted ranges of saturation and not at saturation levels of 100%. In contrast, however, the saturation targets were "a minimum of 99%" in the Gaynon et al study,[28] and "a minimum of 98%" in the Seiberth et

al report.[29] Thus, infants in those 2 series probably had higher average saturation levels than the STOP-ROP supplemental group. To compare the target range of the supplemental arm in STOP-ROP as measured by the Ohmeda 3740 oximeter with these other 2 studies, it could be argued that 1.6 saturation points should be added to the STOP-ROP range to make the saturation monitor readings equivalent. If this is done, the STOP-ROP supplemental range becomes 97.6% to 100% saturation, even closer to the reported series and, therefore, not an explanation of differences.

Another alternative explanation may be in the timing of treatment. If immediate application of the supplemental oxygen at prethreshold diagnosis would provide maximum benefit, it could be argued that use in standard practice would result in earlier and possibly more effective treatment of eyes with prethreshold ROP. Gaynon reports (D. L. Phelps, personal communication, October 1999) that ROP screening was performed at weekly intervals in their series, which could be expected to reduce the number of infants reaching plus disease before beginning oxygen treatment. Screening examinations before prethreshold identification were usually performed every 2 weeks in the STOP-ROP centers, consistent with the AAP recommendations. In addition, the process of obtaining both an independent confirming examination and informed consent of the family or guardians resulted in delays between the first time that prethreshold ROP was observed and the start of the study intervention. In approximately one quarter of the cases, this was >48 hours.

Oxygen requirements go up by ~5 to 9 percentage points when changing to supplemental oxygen from the conventional range, emphasizing that infants truly receive more oxygen when assigned to the supplemental arm. We had not expected that pulmonary events of pneumonia and/or CLD exacerbations were going to be 1.8 times more likely to occur in the supplemental arm. The absolute increase in acute pulmonary events of 7.3% gives a number-needed-to-treat calculation of 1 more pneumonia/CLD episode for each 13.7 infants treated with supplemental oxygen. The ROP progression data give a number-needed-to-treat of 13.2 infants to prevent 1 case of progression to threshold ROP. By this analysis, one could expect ~1 episode of pneumonia/CLD exacerbation for each case of peripheral ablative surgery that might be prevented. That might be regarded as a reasonable trade-off by most neonatologists and ophthalmologists, but the condition of the infants at 3 months' corrected age must also be considered. At that time, 97% of subjects were off the study assigned treatments, and those in the supplemental arm continued to need more oxygen and diuretics, and a greater number remained hospitalized. Our data suggest that the magnitude of any benefit from supplemental oxygen in reducing the need for surgery is likely to be on the order of 7% to 14%, with no reduction in the number of retinal detachments. The potential long-term advantage of avoiding peripheral ablative surgery for ROP is unknown, but to the extent long-term side effects might occur, even a small reduction in surgery rates may be of value. The potential long-term effects, both of costs and to the families, of prolonging hospitalization from worsened lung disease also should be considered.

Our original hypothesis was not only that supplemental oxygen would prove beneficial for the eyes of infants with prethreshold ROP whose pulse oximetry in room air is <94%, but in addition, that it would be beneficial for CLD, resulting in better growth and lower pulmonary vascular resistance.[39,40] However, Supplemental oxygen at a target range of 96% to 99% saturation seemed to have deleterious effects on CLD in some infants, with no change in growth or neuromotor development. Previous reports of an improvement in weight gain and resolution of cor pulmonale with oxygen supplementation could be explained if saturation levels in the control infants of those studies were even lower than the STOP-ROP conventional range. This is certainly possible, because those reports date from periods preceding the routine availability of continuous pulse oximetry. Fortunately, others are investigating this question in a carefully controlled randomized trial in Australia. The Benefits of Oxygen Saturation Targeting Trial is currently enrolling infants in a test of the safety and efficacy of supplemental oxygen for infants with CLD. ROP is not an entry criterion in that study, but will be examined as a secondary outcome (D. Henderson-Smart, personal communication, 1999).

These results provide valuable data for the clinician. The STOP-ROP data clearly demonstrate that oxygen, at saturation levels of 96% to 99% does not increase the severity of ROP in the eyes of infants with prethreshold ROP, even in the 123 eyes with ROP of less than pretheshold severity at randomization. There are no data, however, to suggest that the higher saturation levels are safe for the early immature eye that does not yet have established ROP. The reported data apply only to infants who are well beyond the initial weeks after birth and must not be interpreted as showing safety of supplemental levels of oxygen at younger ages.

The present study does not rule out a potential small reduction in the rate of ROP progression with supplemental oxygen, and a subgroup analysis suggests that supplemental oxygen, as used in this study, may be more effective in pretheshold ROP without plus disease. However, secondary analyses, not prespecified, must be cautiously interpreted and require additional study. The predictive value of various possible definitions of prethreshold ROP have not been systematically studied and reported but could prove very important and should be investigated. The data show a modest deleterious effect of supplemental oxygen on CLD in some infants with more severe lung disease at baseline. Therefore, clinicians must consider which patients might tolerate the added pulmonary risk of supplemental oxygen as a therapeutic intervention for their ROP. If an infant requires saturations of 96% to 99% for cardiopulmonary reasons, fear about causing worse ROP is not a reason to withhold the oxygen. Results from other studies, such as the Benefits of Oxygen Satura-

tion Targeting Trial, may help further our understanding of the effects of supplemental oxygen in infants with CLD.

ACKNOWLEDGMENTS

STOP-ROP was supported by grants from the National Eye Institute, the National Institute of Child Health and Human Development, the National Institute of Nursing Research, several National Institutes of Health General Clinical Research Centers, and local funding sources at many centers. These included: in Rochester, NY, The Delta Gamma Sorority, the Rhea and Raymond White donation, and Research to Prevent Blindness; Boston, MA, support for home oxygen provided by Chartwell Home Therapy, and the New England Medical Center received support from the National Institutes of Health General Clinical Research Center Grant M01-RR00054; and Stanford University received additional support from National Institutes of Health RR 00 070 and National Institutes of Health HD 27 880.

We are indebted to the families who allowed their infants to participate in the STOP-ROP trial, and the dedicated and patient nurses in 71 newborn intensive care units who worked so hard to keep infants within the study target ranges. The Ohmeda Corporation kindly donated the pulse oximeters, and training on their use for all the study centers. We thank Velma Dobson, PhD, for her critical review of the draft manuscript, and Randy Taft of ProFox, Inc, for helping us to develop the laptop computer program that provided feedback on the oximetry.

APPENDIX: THE STOP-ROP PARTICIPATING CENTERS AND MAJOR COMMITTEES

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Chair: Dale L. Phelps, MD; Members: Anne Lindblad, PhD; J. David Bradford, MD; Nancy E. Wood, CCRA; Neal L. Oden, PhD; Cynthia Cole, MD; Brenda MacKinnon, RNC; Anita Yaffe, MSN, MPH; Donald F. Everett, MA; Linda Wright, MD; Cara Krulewitch, CNM, PhD; Additional Writing Committee Members: Beverly S. Brozanski, MD; Terri Young, MD; Mark Scott, MD

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Data Coordinating Center

Principal Investigator: Neal L. Oden, PhD; Anne S. Lindblad, PhD; Co-investigators: Christine Bachy, BS; Stuart H. Berlin, BS; Diane Brandt, BS; Marsha Guzzey, MLT; Linda Henson; Bernadette Jolles, MA; Elaine Stine; Carol Thomas-Sharp, MS, RN; Judith Van Lare; Anita Yaffe, MSN, MPH

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