LACK OF EFFICACY OF LIGHT REDUCTION IN PREVENTING RETINOPATHY OF PREMATURITY

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ABSTRACT

Background Hospital-nursery lighting has been suggested as a factor in causing retinopathy of prematurity. Despite ongoing debate, a causal relation has not been established.

Methods We conducted a prospective, randomized, multicenter study of the effects of light reduction on 409 premature infants with birth weights of less than 1251 g and gestational ages of less than 31 weeks. Two hundred five infants were exposed to reduced light, and 204 to typical nursery lighting. The amount of light reaching the infants' eyes was reduced within 24 hours after birth by placing goggles on the infants that reduced visible-light exposure by 97 percent and ultraviolet-light exposure by 100 percent. The babies wore the goggles until 31 weeks' postconceptional age or 4 weeks after birth, whichever was longer. Once the goggles were removed, ophthalmologists masked to the treatment assignments assessed the infants for retinopathy of prematurity at least biweekly for up to 13 weeks.

Results There were 188 infants in the group that wore goggles and 173 in the control group who survived and were available for follow-up. The mean birth weights were 906 g in the goggles group and 914 g in the control group; the mean gestational ages were 27.4 weeks and 27.2 weeks, respectively. The mean ambient-light level adjacent to the infants' faces was 399 lux for the goggles group and 447 lux for the control group. Retinopathy of prematurity was diagnosed in 102 infants (54 percent) in the goggles group and 100 (58 percent) in the control group (relative risk, 0.9; 95 percent confidence interval, 0.8 to 1.1; $P=0.50$).

Conclusions A reduction in ambient-light exposure does not alter the incidence of retinopathy of prematurity. (N Engl J Med 1998;338:1572-6.)

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RETINOPATHY of prematurity is a leading cause of childhood blindness. It is a disease of the developing retinal vasculature in premature infants. Mild forms regress with little or no loss of visual function; however, more severe forms can lead to retinal scarring and visual loss in the neonatal period. The pathogenesis of the disorder is controversial, but it seems to be related to the infant's environment.

Exposure to light was suggested as a cause of retinopathy of prematurity in the earliest description of this condition,[1] but later studies revealed no association between light exposure and the disease.[2,3] Subsequently, the association between high concentrations of inspired oxygen and retinopathy of prematurity was recognized. The possibility that light could contribute to the development of the disorder was revisited in 1985,[4] and since then there has been an ongoing debate about this possibility.[5-13] However, all the previous studies suffered from one or more of the following limitations: lack of randomization (e.g., the use of historical controls); small numbers of infants at high risk for retinopathy of prematurity; unmasked or uncertified examiners; lack of standardized examination protocols or methods of disease classification; and poorly controlled or unmeasured techniques of light reduction.[2-7] Although the role of light in retinopathy of prematurity is still unclear, lighting levels in the environments of preterm infants have increased.[14] This study was designed to assess the effect of ambient-lighting conditions in neonatal intensive care nurseries on the incidence of retinopathy of prematurity in high-risk infants by using a standardized examination protocol and examiners unaware of the infants' treatment assignments.

METHODS

The study was a clinical trial of standard ambient-light exposure and reduced light exposure in very-low-birth-weight premature infants, designed to test the hypothesis that the reduction of ambient-light exposure in these infants would reduce the incidence of retinopathy of prematurity. Institutional review committees at each center approved the study, and the parents of all the infants gave informed consent.

The premature infants eligible for this study were all at high risk for retinopathy of prematurity on the basis of their weights and gestational ages at birth. All were hospitalized in intensive care units at one of the three study sites. The inclusion criteria were a birth weight of less than 1251 g, a gestational age at birth of less than 31 weeks, admission to a participating neonatal intensive care unit within 24 hours after birth for infants not born at one of the study sites, and parental informed consent within 24 hours after an infant's birth. Exclusion criteria were the presence of a lethal congenital anomaly or a major congenital abnormality of one or both eyes, the lack of full neonatal-intensive-care-unit support, the inability to begin wearing goggles within 24 hours after birth, and the likelihood that follow-up would not continue to 40 weeks' gestational age.

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*The other investigators and committees participating in the LIGHT-ROP Cooperative Group are listed in the Appendix.

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Enrollment began in July 1995 and ended in March 1997. After enrollment, the treatment was randomly assigned by telephone communication with the coordinating center. Randomization was stratified according to center and birth weight (<1000 g or ⩾1000 g).

Study Plan

Light exposure was reduced by placing light-reducing goggles (NoIR Medical Technologies, South Lyon, Mich.) on the infants within 24 hours after birth. These goggles reduced exposure to visible light by about 97 percent and to ultraviolet light by 100 percent without seriously depriving the infants of forms or images. The control group was exposed to the amount of light that was usual for the intensive care unit. Infants wore the goggles until 31 weeks after their conception or 4 weeks after their birth, whichever was longer, at which time the goggles were permanently removed. Other than the goggles, the infants in both groups received the same, customary medical care in the standard lighting environment of the nursery. All the infants undergoing phototherapy for hyperbilirubinemia had their eyes protected in the standard way.

The length of time the infants wore goggles was based on the natural history of retinopathy of prematurity and was chosen so that the goggles were removed before it became necessary to identify cases of severe retinopathy of prematurity that might require surgical intervention.[15] Once the goggles were removed, certified examiners, masked to treatment-group assignment, conducted serial eye examinations according to a predetermined schedule. The first examination was conducted four hours to seven days after the goggles were removed, and at the equivalent time in the control infants. The infants were subsequently examined biweekly until their eyes were fully vascularized, or if retinopathy of prematurity was diagnosed, until they reached 44 weeks' postconceptional age, provided regression was occurring. If an infant was judged to be medically unstable at the time scheduled for the examination, this circumstance was reported to the coordinating center, and the examination was performed at the earliest subsequent opportunity.

The infants' eyes were examined by binocular indirect ophthalmoscopy with scleral depression. Efforts to ensure that the examiners were unaware of the treatment-group assignments included shielding the infants' temples during the first eye examination to cover possible signs that goggles had been worn, using trained research personnel to schedule and assist with the examinations, removing study supplies from the bedside, and discouraging clinical staff and parents from revealing the group assignments.

Before participating in the study, the examining ophthalmologists were certified through the use of a series of paired examinations with an experienced examiner. The results of the paired examinations were sent to another participating center and reviewed for consistency by a third experienced examiner. Agreement on five examinations was required before an ophthalmologist was certified.

Outcomes

Retinopathy of prematurity was classified according to the international classification of retinopathy of prematurity.[16] The study outcome was confirmed disease, which was subdivided into less than prethreshold, prethreshold, and threshold retinopathy of prematurity. Figure 1 shows the way the disease was characterized during the eye examinations. The location was described by zone (I to III), the extent by comparison of the retina with a clock face marked off by hours (1 to 12), and the severity of abnormal vascularization by stage (1 to 3) and by the presence or absence of dilatation of the posterior retinal vessels (referred to as "plus" disease).[16]

The primary outcome of retinopathy of prematurity was defined by the presence of any stage of the disease in any zone, in an area represented by at least three contiguous clock hours, in at least one eye. Confirmation on two consecutive examinations up to seven days apart was required by the study protocol.

After retinopathy of prematurity was confirmed, further eye examinations were done biweekly to determine whether it had progressed to the secondary outcomes of prethreshold retinopathy of prematurity (defined as zone I, any stage; zone II, stage 2 with "plus" disease; or zone II, stage 3) or threshold retinopathy of prematurity (defined as stage 3 disease extending to five contiguous or eight total clock hours in zone I or II, with "plus" disease). The severity of retinopathy of prematurity was classified according to its most advanced progression. Other confirmed retinopathy of prematurity was classified as less than prethreshold. The absence of the disease was determined by continuing examinations until full, normal retinal vascularization occurred.

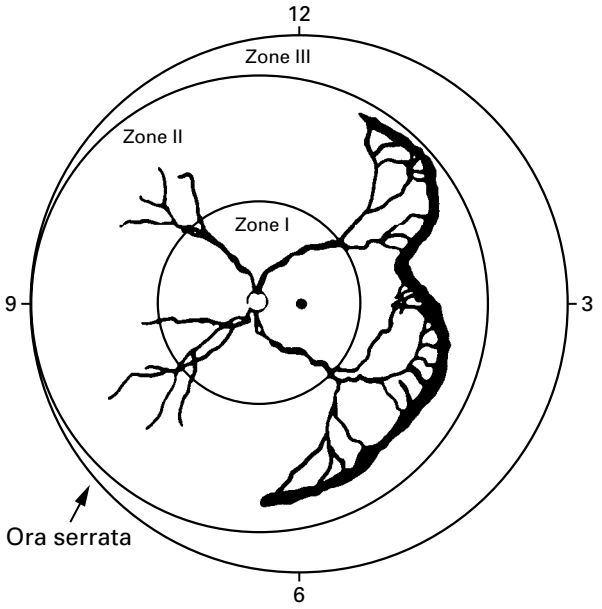

Figure 1. Representation of the Retina, Divided into Zones and Clock-Face Hours, Illustrating an Example of Stage 3 Retinopathy of Prematurity with "Plus" Disease in Zone II, in an Area Corresponding to Five Contiguous Clock Hours.

Stage 3 retinopathy of prematurity (the highest level of abnormal vascularization) is shown extending from approximately one o'clock to six o'clock.

If prethreshold retinopathy of prematurity developed, eye examinations were usually carried out on a weekly basis to monitor progression that might warrant treatment with cryotherapy or laser photocoagulation. In the case of regressing disease, further examinations were done at intervals of two to three weeks.

A complete ophthalmologic examination was performed by an examiner masked to treatment-group assignment six months after term. This examination, which was intended to provide information about later ocular findings should goggles prove beneficial, included assessment of vision and motility; gross anterior-segment examination of the cornea, anterior chamber, iris, pupil, lens, and retina; and measurement of cycloplegic refraction. Of these examinations, the cycloplegic is the most likely to show a possible adverse effect of early wearing of goggles.

Light Monitoring

To characterize nursery lighting conditions, light-meter readings with the sensor facing the ceiling were taken adjacent to each infant's face four times a day, three days a week, before the first eye examination. No attempt was made to control or change nursery practices that would affect the usual care or lighting in the nursery.

Initially, light exposure was measured with a prototype of a

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continuous-monitoring device, but the device proved unreliable. Therefore, commercial light meters (Digital Light Meter RS 180-7133, RS Components, Corby, United Kingdom) were used to record ambient-light levels during the latter part of the study.

Compliance with the Protocol

The study-center coordinator at each site checked the infants at least four times a day, three days each week, to ensure compliance with the treatment regimen. During these visits to the nursery, the coordinator also checked the position of the goggles, assessed the lighting conditions in the nursery, and took measurements with the light meter. The infants were monitored by the coordinator as well as by nursery staff for any untoward problems, such as contact dermatitis, allergy, skin breakdown, or conjunctivitis. If medical problems developed that made it impossible for an infant to continue wearing the goggles, removal was allowed.

Statistical Analysis

For the primary analysis of the effect of light reduction on retinopathy of prematurity, the goggles group and the control group were compared with use of chi-square analysis; 95 percent confidence intervals were calculated for the difference in the percentage of infants with confirmed disease. The relative risk and its confidence intervals are also given. This analysis was supplemented by a logistic-regression analysis to adjust for the effects of gestational age, birth weight, race, and whether the infant was born at a study site to ensure that any observed effect of wearing goggles, positive or negative, was due to light reduction and not due to imbalances in base-line characteristics that were present despite randomization.

The secondary outcomes were compared by chi-square analysis. Similar analyses using logistic regression were done to adjust for base-line characteristics.

RESULTS

Five hundred twenty-five infants were identified as potential participants in the study, of whom 116 were excluded for the reasons shown in Figure 2. The remaining 409 infants were enrolled in the trial; 205 were assigned to wear goggles and 204 to receive the usual care in the nursery without goggles.

In the first 28 days, 46 infants died and 2 could not be followed up. The base-line characteristics of the remaining 188 infants in the goggles group and the 173 infants in the control group who were available for outcome determination were similar, except that fewer infants in the goggles group were not born at a study site ($P=0.02$), fewer had birth weights of less than 750 g ($P=0.15$), and more were black ($P=0.10$) (Table 1). These findings may indicate that the goggles group was at lower risk for retinopathy of prematurity. The median duration of wearing goggles was 28 days (range, 28 to 63 days). The mean light levels measured adjacent to the faces of 65 infants in the goggles group and 68 infants in the control group were 399 lux and 447 lux, respectively ($P=0.14$).

The frequencies of confirmed retinopathy of prematurity in the goggles and control groups were 54 percent and 58 percent, respectively (difference, 4 percent; 95 percent confidence interval, −14 to +7 percent; $P=0.50$) (Table 2). Therefore, light reduction as carried out in this study did not reduce the risk of retinopathy of prematurity (relative risk, 0.9; 95 percent confidence interval, 0.8 to 1.1; $P=0.50$). The combined frequency of prethreshold and threshold retinopathy of prematurity was 15 percent (10 percent and 5 percent, respectively) in the goggles group and 14 percent (9 percent and 5 percent, respectively) in the control group ($P=0.78$). Thus, most infants had less than prethreshold retinopathy.

Subgroup Analyses

No subgroup was identified in which there was a significant difference between the goggles group and the control group (Table 3). Because of the

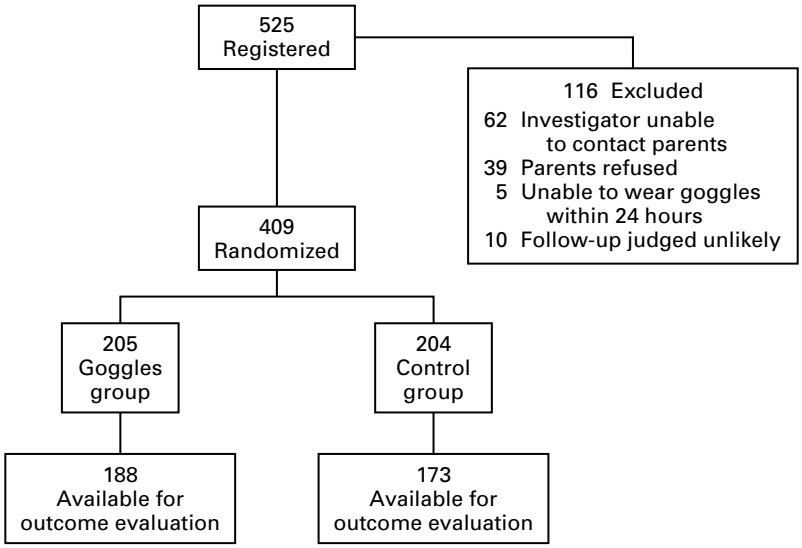

Figure 2. Status of 525 Very-Low-Birth-Weight Premature Infants Considered for the Study of Retinopathy of Prematurity.

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE INFANTS FOR WHOM OUTCOME DATA WERE AVAILABLE.*

CHARACTERISTIC	GOGGLES GROUP (N=188)	CONTROL GROUP (N=173)
	number (percent)	
Birth weight		
<750 g	36 (19)	44 (25)
750–999 g	82 (44)	62 (36)
≥1000 g	70 (37)	67 (39)
Mean (g)	906±181	914±191
Gestational age		
≤27 wk	91 (48)	85 (49)
28–30 wk	97 (52)	88 (51)
Mean (wk)	27.4±1.7	27.2±1.7
Race of mother		
White	50 (27)	51 (29)
Black	53 (28)	36 (21)
Other	85 (45)	86 (50)
Sex		
Male	95 (51)	97 (56)
Female	93 (49)	76 (44)
Born at study site		
Yes	172 (91)	144 (83)
No	16 (9)	29 (17)
Type of birth		
Singleton	143 (76)	138 (80)
Multiple	45 (24)	35 (20)

*Plus–minus values are means ±SD.

TABLE 2. INCIDENCE OF CONFIRMED RETINOPATHY OF PREMATURITY ACCORDING TO SEVERITY AND TREATMENT GROUP.

OUTCOME	GOGGLES GROUP (N=188)	CONTROL GROUP (N=173)
	number (percent)	
Confirmed retinopathy of prematurity	102 (54)	100 (58)
Threshold	9 (5)	9 (5)
Prethreshold	19 (10)	15 (9)
Less than prethreshold	74 (39)	76 (44)
No confirmed retinopathy of prematurity	86 (46)	73 (42)
Retinopathy of prematurity not meeting minimal study criteria*	28 (15)	21 (12)
No retinopathy of prematurity	58 (31)	52 (30)

*Infants had retinopathy of prematurity that either was not confirmed or affected an area represented by less than three clock hours.

TABLE 3. INCIDENCE OF CONFIRMED RETINOPATHY OF PREMATURITY ACCORDING TO BASE-LINE CHARACTERISTICS.*

CHARACTERISTIC	GOGGLES GROUP		CONTROL GROUP		RELATIVE RISK (95% CI)
	number	percent with ROP	number	percent with ROP	
Birth weight					
<750 g	36	83	44	80	1.1 (0.9–1.3)
750–999 g	82	61	62	68	0.9 (0.7–1.2)
1000–1250 g	70	31	67	34	0.9 (0.6–1.5)
Gestational age					
≤27 wk	91	74	85	74	1.0 (0.8–1.2)
28–31 wk	97	36	88	42	0.9 (0.6–1.2)
Sex					
Male	95	54	97	55	1.0 (0.8–1.3)
Female	93	55	76	62	0.9 (0.7–1.1)
Race					
White	50	56	51	65	0.9 (0.6–1.2)
Black	53	53	36	44	1.2 (0.8–1.9)
Other	85	54	86	59	0.9 (0.7–1.2)
Born at study site					
Yes	172	53	144	54	1.0 (0.8–1.2)
No	16	69	29	79	0.9 (0.6–1.3)
Type of birth					
Singleton	143	57	138	59	1.0 (0.8–1.2)
Multiple	45	44	35	54	0.8 (0.5–1.3)
Time of randomization					
6 hr after birth	26	65	21	52	1.3 (0.8–2.1)
7–24 hr after birth	162	53	152	59	0.9 (0.7–1.1)
Total	188	54	173	58	0.9 (0.8–1.1)

*ROP denotes retinopathy of prematurity, and CI confidence interval.

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small imbalances in base-line characteristics, statistical adjustment was done by multiple logistic-regression analysis. Both the unadjusted analysis (odds ratio, 0.9; P=0.50) and the adjusted analysis (odds ratio, 0.9; P=0.75) indicated no significant difference between the two treatment groups.

Six-Month Follow-up

Cycloplegic refraction was measured as part of the six-month follow-up examination. On the basis of this assessment, myopia (defined as the spherical equivalent of at least 0.25 diopter of myopia) occurred in 31 (19 percent) of the infants in the goggles group and 28 (19 percent) of those in the control group (P=1.00). The other ocular findings in the two groups also were similar at the six-month follow-up examination.

DISCUSSION

Exposing premature infants to high levels of inspired oxygen is known to generate free radicals in the retina, which may increase the incidence of retinopathy of prematurity. Ambient-light exposure also causes an increase in free radicals. This action is a basis of the hypothesis of a link between ambient-light exposure and retinopathy of prematurity.

Earlier studies of the relation between these two variables suffered from one or more design flaws. We conducted a randomized trial in which we carefully controlled light reduction and used masked examiners. We found no relation between the use of goggles to reduce the amount of ambient light reaching premature infants' eyes and the incidence of any retinopathy of prematurity. In addition, the six-month ocular examinations revealed no adverse effect of wearing the goggles.

There were small differences in base-line characteristics between the infants in the goggles group and those in the control group: in the goggles group there were fewer infants with birth weights of less than 750 g, more black infants, and fewer infants not born at a study site. These factors together might have tended to increase the risk of retinopathy of prematurity in the control group and bias the study toward a treatment effect. Yet no treatment effect was found.

In designing the protocol, we considered the potential importance of early goggles placement, but given the need to obtain informed consent from a mother immediately after delivery in order to perform such a study, we permitted enrollment for up to 24 hours after birth. However, even in the 47 infants enrolled within six hours after birth, there was no treatment effect. Infants who had goggles placed early had a 65 percent incidence of retinopathy of prematurity, as compared with 52 percent in the control group.

In summary, we found that light reduction does not reduce the frequency of retinopathy of prematurity in infants at high risk for this disorder.

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Dr. Spencer has a royalty agreement with NoIR Medical Technologies, the manufacturer of the light-reducing goggles used in this study.

APPENDIX

In addition to the authors, the LIGHT-ROP investigators and committees were as follows: **Buffalo Center (study headquarters):** Department of Ophthalmology, State University of New York at Buffalo School of Medicine and the Children's Hospital of Buffalo, Buffalo — D.C. Gordon, S. Awner, and M.S. Seligson; **Dallas Center:** University of Texas Southwestern Medical Center, Dallas — L.A. Donahue, D.R. Weakley, C.A. Wilson, R. Vallar, N. Hakimian, and J. Kirby; **San Antonio Center:** Department of Ophthalmology, University of Texas Health Science Center, San Antonio — A.K. Gong, E. von Schulenburg, T.P. Cleland, B.L. Lee, and L.M. Marouf; **National Eye Institute, Bethesda, Md.** — D.F. Everett; **Coordinating Center:** School of Public Health, Coordinating Center for Clinical Trials, University of Texas Health Science Center, Houston — B.R. Davis, B. Tung, and S. Ingerslew; **Data and Safety Monitoring Committee:** — J. Connett, E.A. Palmer, D.L. Phelps, J. Tonascia, B. MacKinnon, and M.A. Bobinski.

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