Light reduction and the electroretinogram of preterm infants

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Abstract

***Aims*—To examine the effects of light on retinal development and function in preterm infants as measured by the electroretinogram (ERG). Secondary outcomes included visual acuity testing, the incidence of retinopathy of prematurity, and general wellbeing, reflected in feeding tolerance, rate of weight gain, and length of hospital stay.**

***Methods*—Eligibility criteria for enrolment were birthweight ⩽ 1250 g and gestational age ⩽ 31 weeks. Sixty one infants were randomly allocated by 6 hours after birth to a control or treatment group which wore 97% light filtering goggles for a minimum of four weeks or until the infant reached 31 weeks postmenstrual age.**

***Results*—There were no significant differences between the two groups in the numbers of electroretinograms performed at 36 weeks of postmenstrual age. Although the sample size was not large enough to exclude clinically important differences in secondary outcomes, no significant differences were observed between the groups in visual acuity testing at 4-6 months corrected age, incidence of retinopathy of prematurity, weight gain, or length of stay.**

***Conclusion*—These data support the safety and feasibility of this intervention. A much larger study will be needed to determine whether light reduction to the eyes of very low birthweight infants will reduce the incidence of retinopathy of prematurity or enhance general wellbeing.**

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Preterm infants are exposed from birth until 40 weeks postgestational age to an extrauterine environment that is very different from the "normal" intrauterine environment. The impact of this on development and the iatrogenic problems that occur in preterm infants is an area of considerable interest.[1] Several studies suggest that environmental light and noise may have deleterious effects on sleep patterns, feeding behaviour, weight gain, and respiratory morbidity in very low birthweight infants.[2 3] In particular, early exposure of the preterm infant's developing retina to light has been an area of concern.[4] Premature infants lack simple adaptive functions to assist in protecting their eyes from light. They have thinner eyelids than term neonates and adults.[5] They have larger pupils as well as a decreased ability to constrict their pupils in response to light exposure at less than 30-32 weeks gestation.[6] Younger infants spend more time with their eyes open despite the intensity of illumination in their environment.[7] Very low birthweight infants may therefore be uniquely susceptible to retinal damage from exposure to bright light.

It has long been suggested that exposure of preterm infants to bright light may have a role in the pathogenesis of retinopathy of prematurity (ROP).[8–11] A large randomised controlled trial of light reduction will be necessary to assess adequately the effect of light reduction on the incidence of ROP. However, concerns about the feasibility and safety of this intervention have been raised by reviewers of a proposal for a large multicentre trial to assess the effect of light reduction on ROP.

Little is known about the effect of light exposure on the development of retinal electrophysiology in premature neonates. The electroretinogram is detectable in preterm infants by 31 weeks postmenstrual age[12] and develops rapidly over successive weeks.[13–15] In term infants visual stimuli are important for the development of normal visual function. Whether visual stimuli in general, and light in particular, affect visual development in infants born before 40 weeks gestation is unknown. Visual acuity correlates better with postmenstrual age than postnatal age, but prematurely born infants have slightly accelerated improvement in visual acuity compared with infants born at term.[16] Mactier *et al* observed postnatal changes in preterm infants' electroretinograms (ERGs) and interpreted these as evidence for light having a role in accelerating the development of the ERG.[15] On the other hand, Leaf *et al*[17] reported no difference in the maturation of the ERG between term and preterm infants matched for postmenstrual age.

We conducted a randomised controlled study to evaluate the effect of shielding the eyes of small preterm infants from light. The purpose of this study was to examine the effects of light on retinal development and function in preterm infants, as measured by the ERG. We also evaluated as secondary outcomes visual acuity testing, the incidence of ROP, and general wellbeing, as reflected in feeding tolerance, rate of weight gain, and length of hospital stay. This study also allowed us to assess the feasibility and safety of specially designed gog-

gles to reduce light exposure to the eyes of high risk neonates.

Methods

The study was conducted at Parkland Memorial Hospital Special Care Nursery from August 1993 to June 1994. The eligibility criteria were birthweight ≤1250 g and gestational age ≤31 weeks determined by the new Ballard exam.[18] Assessment of gestational age was done before randomisation by a neonatology fellow or neonatal intensive care nurse trained to perform the exam. Exclusion criteria were congenital anomalies of one or both eyes, lethal or irreparable congenital anomalies noted at birth, and unlikely viability (infants not receiving full intensive care support). Otherwise eligible infants were not included if staff were not available to randomise the infants within six hours of birth. The study and use of deferred consent were approved by the Institutional Review Board.[19] Infants were randomised before consent to allow the assigned regimen to be implemented shortly after birth when exposure to bright lights often begins. This also allowed the mother partially to recover from the effects of labour, delivery, and intrapartum anaesthesia. If consent had not been obtained by 18-24 hours of age, the infant was withdrawn from the study.

Infants were randomly allocated to treatment or control groups by sequential sealed opaque cards. The treatment was initiated by the admitting nurse one to six hours after birth. Enrolment was stratified by race (black or non-black) and birthweight (250 g increments) because of the possible protective effect of dark pigment on retinal light damage and the increased risk of ROP with decreasing birthweight. Twins were assigned to the same study group; only the firstborn surviving twin was included in the analysis.

No attempt was made to regulate environmental light exposure other than by treatment assignment. The neonatal unit at Parkland has relatively bright illumination from large windows and overhead fluorescent lighting. At the discretion of the bedside nurses, the overhead lights were occasionally partially dimmed and blankets were occasionally draped over the infants' incubators or faces. There was no systematic effort to use cycled lighting. Light filtering goggles (NoIR Medical Technology, South Lyon, MI, USA) were used for light reduction in the treatment group. The goggles were 97% effective in filtering light with a neutral density filter which still permitted form vision. The goggles have been used before in a pilot study conducted in Buffalo and Dallas.[20] The goggles were placed in the first six hours after birth and remained in place at least 23 hours a day. Goggles were briefly removed once each nursing shift (every 8 or 12 hours) so that the infants' eyes could be assessed and any complication from the goggles could be recorded. Standard eye patching for infants undergoing phototherapy was performed in infants in both groups. For infants in the treatment group, goggles were replaced once phototherapy had been discontinued. A form documenting goggle compliance was kept at the bedside. Removal time and replacement time were noted as well as the reason for removal. Removal was allowed for parent–infant interaction as well as assessment of the eyes by caretakers, but was limited to one hour a day. The infants were withdrawn from the study for protocol violation if the goggles remained off longer that 24 consecutive hours. The goggles were to remain in place for a minimum of four weeks or until the infant reached 31 weeks postmenstrual age, whichever was longer. Staff providing clinical care for the infants and those collecting the clinical outcome data were not masked to study group assignment.

Clinical data were collected prospectively by a neonatology fellow and trained research nurses using extensive written definitions for diseases and complications.

ELECTRORETINOGRAM

When the infants reached 35 weeks postmenstrual age they were prepared for an ERG, if they were determined to be medically stable by the attending neonatology faculty member or fellow. The pupils were dilated with two drops of cyclomydril 1% in each eye 30 and 15 minutes before onset of dark adaptation. They were then fed, swaddled supine, and placed in a dark room with pulse oximetry monitoring. Dark adaptation was done for a minimum of 20 minutes. At the end of dark adaptation, two drops of proparacaine hydrochloride were instilled in each eye under red light to anaesthetise the cornea. A ground electrode was placed on the forehead and a premature infant Burian-Allen bipolar contact lens electrode, filled with methylcellulose, was placed on the eye. Stimuli (10 μs flashes) were delivered through a Ganzfeld dome lowered over the crib. The dome contained a small aperture for viewing the infant under dim red light during the session. Responses were recorded only when the pupil was clearly visible within the contact lens electrode.

ERG analysis

Full field ERGs were obtained from the cornea using a Burian-Allen bipolar contact lens electrode, amplified (gain 10 000; 3 dB down at 2 and 300 Hz) and averaged (n=20) with a minicomputer, using software to reject sweeps containing artefacts about twice the signal amplitude. Standard protocol[21] stimuli were: (1) a short wavelength stimulus to elicit a dark-adapted rod response; (2) a maximum intensity white response to elicit a mixed dark-adapted rod and cone response; (3) 30 Hz flicker to isolate a cone response; and (4) a maximum intensity white stimulus on a 34 cd/m^2 background to elicit a cone response. Rod responses were also obtained in ascending order to an intensity series of short wavelength (λ_{max} 450 nm; bandwidth 55 nm) stimuli. The interstimulus interval was varied from 1 to 5 seconds as a function of retinal illuminance to avoid light adapting the infants. Rod responses were isolated at high stimulus illuminances by

Table 1 Patient characteristics at enrolment, and clinical outcomes

	Control (n=26)	Goggle (n=24)	P value
At enrolment:			
Birthweight (g)	914 (40)	964 (37)	
Gestational age (weeks)	28.1 (0.3)	27.8 (0.4)	
Race (black/other)	15/11	15/9	
Gender (female/male)	14/12	13/11	
After enrolment:			
HMD (yes/no)	13/13	16/8	0.36
Duration of ventilation treatment (days, median)	7	6	0.80
Duration of oxygen treatment (days, median)	43	39	0.93
IVH any grade (yes/no)	8/18	7/17	0.85
IVH ⩾ grade 2 (yes/no)	5/21	5/19	1.00

computer subtracting cone responses to phototpically matched long wavelength stimuli.[22] Rod ERG amplitudes as a function of retinal illuminance were analysed by finding the parameters of the best fit Naka-Rushton function: $V/V_{max} = I/(I+k)$ where V = rod peak-to-peak amplitude, V_{max} = maximum rod amplitude, I = retinal illuminance, and k = retinal illumanance at half amplitude. Rod threshold (2.0 μV criterion) was derived from the Naka-Rushton parameters: log threshold = log k + 0.3 –log(V_{max} –2).

Cone responses to the series of long wavelength stimuli were used to determine cone ERG threshold. The cone threshold (2.0 μV) criterion was derived from a linear regression of log cone amplitude on log retinal illuminance. The staff recording and interpreting the ERGs were blinded to study group assignment.

Examinations of visual acuity were performed on those infants who completed the study protocol and attended the follow up clinic at the Children's Medical Center at Dallas. The visual acuity exam was scheduled at 4 to 6 months age (adjusted for prematurity). Visual acuity was assessed with a preferential looking technique[23] by a nurse trained to use the Teller Acuity Cards (Vistech Consultants, Inc., Dayton, OH, USA). This examiner was masked to the infants' study group assignment. All acuities were converted to a (log minutes of arc resolution) log MAR scale for analysis. Log MAR acuities were compared with published binocular norms.[24]

Study subjects received routine ophthalmological screening exams for retinopathy of prematurity. The first exam was performed by six weeks after birth or by discharge from the hospital. Screening exams were performed by ophthalmology house staff and retina fellows; examiners were masked to the infants' study group assignments. Subsequent examinations were performed every one to three weeks as medically indicated. Classification of ROP followed the International Classification of ROP[25] and the modifications used in the multicentre study of cryotherapy for ROP.[26]

The duration of the study was prospectively planned but constrained by the opportunity for patient enrolment during the last year of a research fellowship training period. Sample sizes were estimated for $\alpha=0.05$ and $1-\beta=0.80$. Using available standard deviations from ERGs in preterm infants,[14] a sample size of 20 per group would be sufficient to detect a difference in log k of 0.15 log unit, in log V_{max} of 0.2 log unit, and in log rod threshold of 0.22 log unit.

STATISTICAL ANALYSES

Results for normally distributed outcomes are reported as mean (SEM). Analysis of the ERG and visual acuity data, birthweight, and estimated gestational age were done using Student's *t* test. Duration of oxygen treatment, ventilator treatment, and hospital stay are reported as medians and were analysed using the Rank Sum test. Analysis of race, sex, hyaline membrane disease, intraventricular haemorrhage, and ROP were done using χ^2 or Fisher's Exact test. SigmaStat for Windows (Jandel Scientific Software, San Rafael, CA, USA) was used for the analyses.

Results

There were 135 infants ⩽ 1250 g born at Parkland Memorial Hospital during the study period. Of these, 61 completed randomisation and enrolment and 46 infants completed the primary outcome variable (ERG). The flow of all eligible participants is shown in fig 1. Of the 11 infants excluded because they were assessed to be non-viable, 10 died at 0-8 days of age and one survived until discharge.

Patient characteristics at enrolment and clinical outcomes are shown in table 1. There were no significant differences between the groups.

The ERGs were performed at 36.6 (0.3) and 36.2 (0.3) weeks postmenstrual age in the control and goggle groups, respectively. The postnatal age at which the ERGs were performed were 61 (3) and 59 (4) days in the control and goggle groups, respectively. In the goggle group, the interval between goggle removal and ERG was 28 (3) days (range 0-54). The ERG data are shown in table 2. There were no significant differences between the two groups in any of these variables.

The ERG standard protocol parameters are shown in table 3. To compensate for reduced

Table 2 ERG data (mean(SEM))

	Control (n=23)	Goggle (n=23)	95% Confidence interval for difference	P value
Postnatal age ERG done (days)	61 (3)	59 (4)		0.72
Gestational age ERG done (weeks)	36.6 (0.3)	36.2 (0.3)		0.33
Duration of goggle wear		30.9 (1.2)		
Duration of standard nursery light exposure before ERG (days)	61 (3)	28 (3)		< 0.001
Rod log threshold (log scot td-sec)	−0.11 (0.08)	−0.04 (0.09)	−0.31 to 0.17	0.56
Rod log k (log scot td-sec)	0.86 (0.08)	0.80 (0.09)	−0.18 to 0.30	0.62
Rod log V_{max} (log μV)	1.32 (0.04)	1.20 (0.04)	−0.004 to 0.24	0.06
Cone log threshold (log phot td-sec)	−0.11 (0.06)	−0.07 (0.06)	−0.21 to 0.13	0.62

Table 3 ERG standard protocol parameters (mean(SEM))

	Control (n=23)	*Goggle (n=23)*	*95% Confidence interval for difference*	*P value*
Rod response (blue)[1]				
Amplitude (μV)	11.0 (1.1)	8.6 (0.8)	−0.4 to 5.2	0.10
IT (msec)	93.0 (3.7)	93.4 (3.8)	−11.0 to 10.2	0.94
Maximal mixed rod/cone response (white)[2]				
Amplitude (μV)	35.8 (3.6)	32.4 (3.3)	−6.4 to 13.3	0.49
Cone response (30 Hz flicker)[3]				
Amplitude (μV)	3.77 (0.54)	3.97 (0.57)	−1.8 to 1.4	0.80
IT (msec)	39.7 (0.8)	41.6 (1.0)	−4.4 to 0.7	0.15
Light-adapted cone response (white + background)[4]				
Amplitude (μV)	25.4 (2.2)	23.2 (2.3)	−4.4 to 8.7	0.51
IT (msec)	45.3 (1.4)	45.9 (1.5)	−4.7 to 3.6	0.80

[1] 0.7 log scotopic troland-sec (setting 1; Wratten 47A filter).
[2] 2.0 log photopic troland-sec (setting 16; no filter).
[3] 1.3 log photopic troland-sec (setting 4; no filter).
[4] 2.0 log photopic troland-sec (setting 16; no filter; 3.0 log photopic background).

Table 4 Secondary outcomes

	Control (n=26)	*Goggle (n=24)*	*95% Confidence interval for difference*	*P value*
Time to reach 1500 g (median in days)	46	37		0.21
Time to reach full feedings (median in days)	28	18		0.12
Length of stay in hospital (median in days)	79	66		0.32
ROP any stage (yes/no)	8/18	7/17	0.27 to 4.35	0.85
Pre-threshold ROP (yes/no)	1/25	1/23	−0.01 to 75.25	> 0.999

rod sensitivity in very low birthweight neonates, a higher retinal illuminance than the clinical standard[21] was used to elicit the response. The retinal illuminances corresponding to each stimulation condition were calculated for each infant using that individual's measured pupil size. Median pupil size was 6.0 mm and the list below the table uses that measurement to illustrate typical conditions. Grass photostimulator settings and spectral filter (if any) are shown within parentheses.

Visual acuity exams were performed at 3 to 13 months postmenstrual age. Visual acuity results were converted to logMAR scale and expressed as the difference from published norms for age[24] (adjusted for prematurity). The difference from the norm was −0.199 (0.084) [mean (SEM)] logMAR for the control group (n=14) and −0.159 (0.084) [mean (SEM)] logMAR for the goggle group (n=12). There was no significant difference between the groups (P=0.74). It should be noted that a dif-

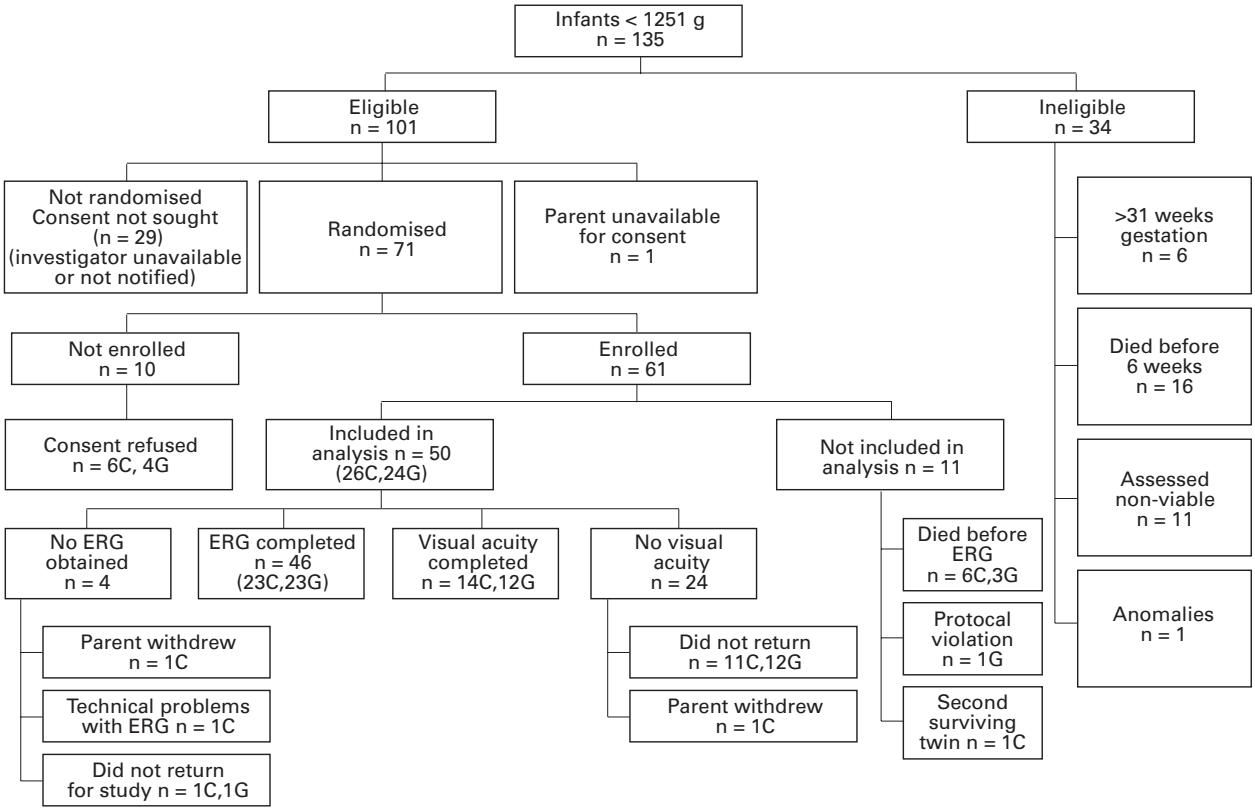

Figure 1 Flow diagram of eligible participants: C = controls, G = goggles.

ference of less than 0.17 logMAR could not be reliably detected with this sample size. In a separate analysis including only those infants tested at 4-6 months postmenstrual age, there were again no significant differences between the groups (P=0.82). The difference from the norm was −0.153 (0.116) [mean (SEM)] logMAR for the control group (n=9) and −0.187 (0.089) [mean (SEM)] logMAR for the goggle group (n=9). Other secondary outcomes for the study are shown in table 4. There were no significant differences between the groups in other clinical outcomes, although the sample size was not large enough to exclude clinically important differences in visual acuity or other secondary outcomes.

Discussion

In this study we have shown the feasibility of using facial goggles to decrease light exposure to the eyes of very low birthweight infants. The protocol violations were minimal (n=1). Parents were very accepting of the intervention. Only one mother withdrew from the study after randomisation; permission was denied for the ERG exam after the intervention period had been completed. There were no complications identified as a result of wearing the goggles.

Because very low birthweight infants are often exposed to bright procedure lights immediately after birth, we wanted to begin the intervention for this study as soon as possible after birth. The delayed consent strategy was justified because of the benign nature of the intervention (placing goggles), variable exposure to light under non-study conditions, the dubious validity of consent obtained during labour, and improved maternal comprehension and ability to participate in decision making achieved by allowing the mother time to recover from the delivery and analgesia or anaesthesia administered before a delivery. The proportion of mothers who agreed to participate in the study was relatively high (85%), and there were no problems with maternal acceptance of our delayed consent strategy. This experience suggests that use of deferred consent should be considered where appropriate in other neonatal trials.[27 28]

Mactier *et al*[15] found changes in amplitude and B-wave latency in response to light exposure by obtaining ERGs shortly after birth and then after routine light exposure. Because there were no "control" infants who were not exposed to light, the effect of light exposure could not be distinguished from maturation or from other factors in the infants' care during the time period or the effect of time itself. In our study patients in each study group had ERGs performed at the same postmenstrual age and at the same postnatal age. The only differences between our two groups of patients was duration of exposure to nursery lighting, and there were no significant differences in ERG findings related to duration of light exposure.

The incidence of ROP observed in our study (15/50 or 30%) was considerably lower than the 66% incidence observed for a similar group of patients in the Multicenter Cryotherapy Study.[29] There are several potential explanations for this difference. Our study was conducted seven years after the Multicenter Cryotherapy study. This multicentre study remains the most comprehensive published review of the incidence and time course of ROP, but many clinical practices (the use of oximetry, surfactant administration, nutrition practices, the use of prenatal and postnatal steroids) have changed over the intervening years; the effects of these changes in practice on the incidence of ROP are unknown. ROP was not a primary outcome for our study. In our study, there was no attempt to certify the ophthalmologists or confirm findings with a second examination. The examinations were performed according to standard practice in our unit; in general, the examiners were less experienced than those conducting the examinations in the Multicenter Cryotherapy Study. Infants are being discharged from the hospital earlier than in previous years, and extraordinary measures to enhance compliance with follow up ophthalmology appointments were not in place during this study.

Normative data have been established for neonates undergoing visual acuity testing with Teller Acuity Cards.[16 30] By this testing method, all of the infants in our study had normal visual acuity at their four to six month follow up visit. Thus we were unable to detect any deleterious effect of goggle wear on visual development in the infants enrolled in this study. We found no significant effect on general wellbeing, as determined by weight gain or length of stay, although the medians for these outcomes tended to favour the goggle group.

We found no deleterious effect of light reduction on visual development of very low birthweight infants, as measured by the ERG or visual acuity testing. These data support the safety of this intervention as well as the feasibility of this method of light reduction in this group of infants. A much larger study will be needed to determine whether light reduction to the eyes of very low birthweight infants will reduce the incidence of ROP or enhance general wellbeing.

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