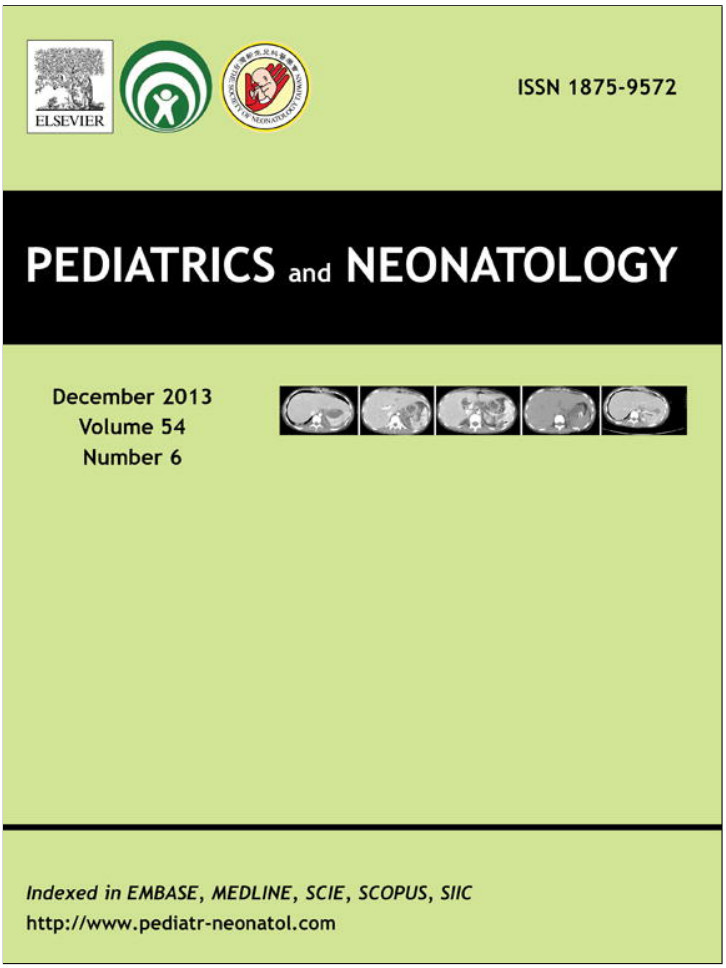

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ORIGINAL ARTICLE

"Oxygen with Love" and Diode Laser Treatment Decreases Comorbidity and Avoidable Blindness due to Retinopathy of Prematurity: Results Achieved in the Past 12 Years

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Aim: To determine whether the "Oxygen with Love" (OWL) and diode laser treatment provided in a neonatal intensive care unit has reduced the risk of avoidable blindness caused by retinopathy of prematurity (ROP) over the past decade.
Materials and methods: A prospective observational cohort study was performed, in which 351 infants were examined for ROP. The inclusion conditions were as follows: preterm infants, birthweight <1500 g or <32 weeks' gestational age, and birth between 1 Jan 2000 to 31 August 2012. From mid-2009, the OWL program was implemented and the ventilation protocols for such infants were amended. We tested whether the incidence of unfavorable structural outcomes of ROP had decreased following these changes.
Results: From 2004 to 2012, the survival rates of younger children increased ($p < 0.003$). From 2005 to 2012, laser treatment rather than cryotherapy was applied, and the incidence of unfavorable structural outcomes of ROP fell from 13% to 5.6% (not significant). From 2009 to 2012, the incidence of ROP decreased from 55% to 29% ($p < 0.002$). From 1 August 2009 to

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31 August 2012, there was less need for ablative treatment for premature infants, with the rate falling from 11.81% to 3.9% ($p < 0.03$). This improvement was significantly associated with a reduction in the number of days of intubation ($p < 0.0017$), lower rates of sepsis ($p < 0.003$), and improvements in postnatal weight gain ($p < 0.0002$).
Conclusion: The introduction of the OWL program, together with lower rates of sepsis, improvements in postnatal weight gain, and the use of diode laser treatment, has reduced the incidence of unfavorable structural outcomes of ROP.

1. Introduction

Retinopathy of prematurity (ROP) and cortical blindness are the most common causes of blindness in premature infants.[1] To minimize the rate of avoidable blindness due to ROP, two possible courses of action may be taken: continuing improvements in neonatal care, to reduce the incidence of infants with ROP and treatable severe ROP[2–4]; and, with respect to the ophthalmologist, the detection of all treatable cases and continuing improvements in techniques and modes of treatment.[5–8]

The present study aimed to determine whether the modifications introduced in our neonatal intensive care unit (NICU) have achieved objective improvements in the care and treatment of ROP, and if so, which variables are of most influence.

2. Materials and Methods

We studied 351 newborn infants included in the retinopathy examination protocol for premature infants at San Cecilio University Hospital (Granada, Spain) over a study period from January, 2000 until August 31, 2012. The inclusion conditions were as follows: preterm infants of birthweight <1500 g or <32 weeks' gestational age, and birth between 2000 and 2012.

The following variables were included in the study: gestational age at birth, birthweight, peak ROP stage for each newborn, the need for treatment, the structural outcome of treatment, and the type of treatment used—cryotherapy (2000–2004) or laser (2005–2012). The change of treatment criterion was made (from CRYO-ROP to ET-ROP) in 2004. Comorbidity was defined as any event, complication, or treatment that is not expected in a child born healthy in a natural childbirth. The following variables were used to assess comorbidity: the presence of sepsis, the stage of hyaline membrane disease, persistent ductus arteriosus, the number of days of intubation, the degree of cerebral hemorrhage, the need for blood transfusion, cesarean section, surfactant therapy, maternal hypertension, the need for exchange transfusion, and extracranial bypass surgery. A point was assigned to quantify the comorbidity of each of these events, and the sum of the scores for each of the variables gave the total comorbidity score for each premature infant.

Table 1 shows the distribution of patients in this study. The same ophthalmologist was responsible for eye examinations from 2000 to 2012. Staging of ROP was based on retinal examination prior to discharge, with severe ROP stage 0 = no ROP, ROP incidence = ROP stage > 1, ROP > 2 = progression ROP, severe ROP defined as stages 3–5.[9] The eye was classified as having an unfavorable outcome in ROP if at least one of the following findings was present: a retinal fold involving the macula, a retinal detachment involving zone I of the posterior pole, and retrolental tissue, or a "mass."[10]

In order to distribute the number of newborn infants evenly within the study interval, the sample was divided into three time periods: 2000–2003, 2004–2008, and 2009–2012. From August 2009 to 2012, a series of organizational changes were introduced, including the widespread application of "Oxygen with Love" (OWL)[11–13] and the use of ventilation volume guarantee level techniques and noninvasive ventilation,[14,15] raising awareness among the staff of the neonatal unit of the need for newborns to gain at least 7 g of body weight per day during the first month of life.[16] This was accompanied by improvements in clinical practice to reduce the risk of sepsis and the number of transfusions needed.[17,18]

As part of the OWL program, intended for pediatricians, nurses, and respiratory therapists, the oxygen management policy of the NICU was revised as follows: for very low birthweight (VLBW) infants, oxygen saturation (SpO_2) target range of 85–93% from birth to 36 weeks' postmenstrual age, a standardized bedside oximeter alarm setting for all VLBW infants, and guidelines for managing low and high

Table 1 Study of the retinopathy of prematurity program in three time periods, showing the number of infants requiring ablative treatment of the retina and the number presenting an unfavorable structural outcome, by cryotherapy or laser treatment.

Period	*n*	Treatment		Unfavorable outcome	
		Cryotherapy	Laser	Cryotherapy	Laser
2000–2003	105	11	0	1	0
2004 to July 2009	148	4	15	1	1
August 2009 to 2012	97	0	4	0	0

Table 2 Mean values for weight, gestational age, retinopathy of prematurity, and associated comorbidity, together with the rate of unfavorable structural outcomes.

	2000–2003	2004–2008	2009–2012
Gestational age (wk)	30.4	29.6**	29.59**
Weight (g)	1410	1241**	1240***
Comorbidity	4.5	5.3**	4.86
ROP ≥2	29/105 (28%)	46/130 (35%)	16/115 (14%)***
ROP ≥1	52/105 (49%)	71/130 (55%)	30/115 (26.1%)***
Unfavorable structural outcomes	1/11 (9%)	2/14 (14%)	0/9 (0%)

*$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

alarms. The NICU staff were trained in small group sessions for oxygen prescribers (MDs and nurses) and bedside oxygen providers (nurses and respiratory therapists). The session focused on oxygen toxicities in premature infants and details of the new oxygen policy in the NICU. Policy compliance checks included VLBW oximeter alarm limit audits three times per day and continuous oximeter downloads to assess achievement of the SpO_2 goals.

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The statistical mean and standard deviation (SD) were obtained for each factor, and these values were compared for each of the three time periods. The Student *t* test was applied to compare the means, and the Chi-square test was used to compare the qualitative variables.

3. Results

The sample consisted of 351 children identified by screening for ROP in the periods from January 1, 2000 until December 31, 2003 ($n = 105$), from January 1, 2004 until July 31, 2009 ($n = 148$) and August 1, 2009 until August 31, 2012 (n = 98).

Table 2 shows the data for the descriptive variables of the newborns for each study interval. In 2000–2003, the infants were more mature, with greater gestational ages and higher birthweights than those born in the following study periods. These findings explain the significant increase in comorbidity of newborns in the later intervals ($t = 2.61$, $p = 0.0096$). Of note is the finding that, despite the increased comorbidity in 2004–2008 compared with the period 2000–2003 ($t = 3.22$, $p = 0.0014$), there was no significant increase in the incidence of ROP.

From 2009 to 2012, a series of organizational changes were introduced, including the widespread application of the OWL program (on best practice in oxygen use in hospitals),[12,13] raising awareness among neonatal staff of the need for newborns to gain at least 7 g body weight per day during the first month of life[16] and to achieve improvements in clinical practice to reduce the risk of sepsis and the number of transfusions needed.[17,18] We observed Pearson correlation coefficients of 0.21 ($p < 0.001$) and 0.23 ($p < 0.001$), respectively, between the number of sepsis events and the number of transfusions versus the development of retinopathy.

Table 3 The retinopathy of prematurity program: results obtained following the improvements made since August 2009 (fewer days of intubation, a higher 5-minute Apgar score, a lower rate of nosocomial sepsis, and increased postnatal weight gain).

	January 2000–July 2009	August 2009–August 2012
Intubation days (mean, SD)	8.14 (11.88)	3.56 (8.55)**
Days of oxygen supplementation (mean, SD)	33.1 (63)	30.2 (31)
Apgar score at 1 minute (median, SD)	6 (2.46)	6 (2.27)
Apgar score at 5 minutes (median, SD)	7 (2.49)	8 (1.66)*
Blood transfusions, *n* (%)		
Not performed	127 (50.2)	54 (66)
Present	126 (49.8)	43 (44)
Sepsis, *n* (%)		
Absent	161 (64)	74 (76)*
Present	92 (36)	23 (24)
Cesarean, *n* (%)		
Not performed	81 (32)	16 (21)
Performed	172 (68)	61 (79)
Weight gain ≥7 g/d		
Absent	68 (27)	6 (6.2)***
Present	185 (73)	91 (93.8)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
SD = standard deviation.

In this period, there was no significant reduction in comorbidity compared to the previous period ($t = 1.36$, $p = 0.09$) in preterm infants with a similar gestational age and birthweight. However, the changes in the management of these children led to a statistically significant reduction in the incidence of ROP ≥ 1 [$\chi^2 = 19.3$, $p = 0.0001$, odds ratio (OR) = 0.29, 95% confidence interval (CI) 0.16—0.52], and its progression ROP ≥ 2 ($\chi^2 = 13.8$, $p = 0.0002$, OR = 0.3, 95% CI 0.15—0.58). We have no data on the infants' caloric intake prior to 2009, but from 2009 onward we observed an average caloric intake in the first 14 days of life of 1204 kcal (SD 157 kcal) in infants without retinopathy, and of 1365 kcal (SD 188 kcal) in those who developed retinopathy, with no significant differences between the groups. We observed a correlation coefficient of 0.30 ($p < 0.001$) between the degree of retinopathy and a weight gain of greater than 7 g per day.

Regarding ablative treatment for ROP, 2 of 15 of the outcomes were adverse in premature infants with threshold ROP given cryotherapy. When laser treatment was applied for prethreshold and threshold ROP, only 1 of 19 of outcomes was adverse. In our sample, the treatment outcomes did not differ significantly between cryotherapy and laser treatment.

From January 1 of 2000 until July 31, 2009, 30 of the 253 children included in the ROP program at our hospital required treatment. From August 2009 to February 2012, 97 children were included in the same program, and only four required treatment. The risk of retinopathy was significantly lower during this latter period, and a significantly lower percentage of children needed retinal ablation treatment ($\chi^2 = 3.94$, $p = 0.02$, OR = 0.32, 95% CI 0.11—0.95).

On comparing the periods 2000 to July 2009 and August 2009 to February 2012, we observed a lower percentage of sepsis ($\chi^2 = 4.53$, $p = 0.03$, OR = 0.54, 95% CI 0.31—0.96), fewer days of intubation [$t = 4.0$, $p < 0.001$, degrees of freedom (df) 241], a higher 5-minute Apgar score ($t = 2.54$, $p = 0.01$, df 260), and a higher percentage of premature infants gaining $\geq$7 g/day at 4—6 weeks of age ($\chi^2 = 16.8$, $p < 0.0001$, OR = 0.18, 95% CI 0.006—0.44) during the latter period (Table 3).

With respect to unfavorable structural outcomes, the following calculations were carried out, for the three study periods (see Table 1): % infants presenting unfavorable structural outcome = (% premature infants needing retinal ablation) $\times$ (% unfavorable structural outcomes after cryotherapy or laser treatment).

(A) Period 2000—2003:

$$A = 10.48\%\,(\text{retinal ablation}) \times 13.3\%\,(\text{cryotherapy}) = 1.4\%$$

(B) Period 2004 to July 2009:

$$B1 = 12.84\%\,(\text{retinal ablation}) \times 13.3\%\,(\text{cryotherapy}) = 1.71\%$$

$$B2 = 12.84\%\,(\text{retinal ablation}) \times 5.26\%\,(\text{laser}) = 0.68\%$$

(C) Period August 2009 to August 2012:

$$C = 4.12\%\,(\text{retinal ablation}) \times 5.26\%\,(\text{laser}) = 0.22\%$$

The relative risk of an unfavorable structural outcome thus was calculated as: $(1.4 - 0.22/1.4) = 84.28\%$.

In summary, the relative risk of an unfavorable structural outcome for ROP was 84% lower in the final period (August 2009 to August 2012) than in the first one (2000—2003), due to the lower number of premature infants requiring treatment and because outcomes improved with the use of diode laser treatment.

4. Discussion

During the period 2000—2003, infants with a greater birthweight and higher gestational age than in subsequent years were included in the ROP program. As the inclusion criteria remained unchanged during these years, we conclude that survival rates improved in the subsequent periods of 2004—2008 and 2009—2012. This increase in the survival of infants of less than 28 weeks' gestation is also found in other time series studies of ROP outcomes over 9—10 years.[19,20]

Since 2004, our study sample has reflected a reduction in the mortality rates of preterm infants admitted to the hospital. Those enrolled in the ROP protocol from 2004 to 2012 were more immature and presented with greater comorbidity, but despite this the incidence of ROP did not increase. In 2005, diode laser treatment for ROP was introduced, and this technique has reduced the rate of poor outcomes, although the difference with respect to cryotherapy is not statistically significant. From 2009, the comorbidity rates of premature infants fell, as did the rate of sepsis and the number of days of intubation required, whereas the rate of postnatal weight gain increased. These improvements in clinical practice produced a significant reduction in the incidence of ROP and in the number of infants with severe ROP treatable by retinal ablation.

Corroborating our results, Hellström et al[21] related poor weight gain during the first weeks of life with an increased risk of retinopathy. These authors observed an association between the increased risk of retinopathy and a birthweight below the 25th percentile, and with subsequent poor weight gain. Stahl et al[22] reported pathophysiologic information relating deficient postnatal nutrition and low weight gain to more prolonged retinal vascularization and poorer visual outcome.

The strict control of oxygen saturation and supplementation in recent years has reduced the incidence of ROP in children screened for the disease to 15—30%.[8,10,23,24] From 2009 to 2012, the implementation of the OWL program in our NICU significantly reduced the number of days of intubation required and the rates of sepsis, and was also associated with higher numbers of infants with adequate postnatal gain and an increased 5-minute Apgar score. However, another study concluded that advances in obstetric and neonatal care were responsible for reducing the incidence of severe ROP.[25]

In some ROP series, early treatment of prethreshold ROP in zone I has been implemented.[7] Subsequent improvements have also been obtained from a more aggressive treatment of ROP,[26,27] the use of further laser sessions, even when active avascular islets remain, and the application of intravitreal bevacizumab.[28] These measures have

led to excellent rates of structural outcome, with only 4—5% adverse effects.[7,28]

The improvements made to the ROP program at our hospital in the past 3 years have produced the results described here. Aspects such as the lower incidence of infection and sepsis, and improved infant nutrition, which have no direct relationship with the OWL program, have also helped to improve results in the treatment of ROP.

In conclusion, the actions implemented to improve pediatric and ophthalmologic care have reduced the risk of unfavorable structural outcomes in ROP by 84%, due particularly to improvements in oxygen monitoring (the OWL program) and the diode laser treatment for retinal ablation.[29]

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