

Oxygen Monitoring Reduces the Risk for Retinopathy of Prematurity in a Mexican Population

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Key Words

Retinopathy of prematurity · Oxygen · Extremely preterm infants · WINROP algorithm

Abstract

Background: Retinopathy of prematurity (ROP), a potentially blinding disease, affects preterm infants. High levels of oxygen saturation are a well-known risk factor for ROP. **Objectives:** To assess the frequency of ROP type 1 needing treatment after improved oxygen monitoring (2011) in a Mexican preterm population selected for WINROP analyses and to retrospectively revalidate WINROP, an online surveillance system identifying infants at risk of developing ROP type 1. **Methods:** Preterm infants born with birth weight (BW) <1,750 g and/or at gestational age (GA) ≤34 weeks, screened for ROP in 2012–2014 at the Hospital Civil de Guadalajara, Mexico were included (n = 151). Eighty-five infants with GA <32 weeks qualified for WINROP analyses. GA, BW, maximal ROP stage, ROP treatment and weekly weights were recorded. The results in the present study were compared to those of a previous WINROP study in the same hospital (2005–

2010; n = 352). **Results:** In the present WINROP cohort, 11.8% of the infants born at GA <32 weeks received treatment compared to 51.0% of the infants in the previous WINROP cohort. One infant (3%) born at GA ≥32 weeks received treatment during the present study period compared to 35.6% during the previous period. WINROP displayed 80.0% sensitivity in infants born at GA <32 weeks in the present study compared to 84.7% in the previous study. **Conclusions:** Uncontrolled oxygen supplementation is the major risk factor for severe ROP in infants born at GA ≥32 weeks. After improved oxygen monitoring, the frequency of ROP treatment was dramatically reduced at the Hospital Civil de Guadalajara, Mexico.

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Introduction

Retinopathy of prematurity (ROP) is a potentially blinding disease that affects preterm infants around the world [1]. Severe ROP may lead to retinal detachment and blindness, which usually can be prevented by timely detection and prompt treatment. Depending on survival

rates for preterm infants and the quality of prenatal and neonatal care, the proportion of childhood blindness due to ROP varies from 0% in some countries to nearly 40% in others [2]. With less advanced neonatal care, more mature infants are affected, which has led to different national screening criteria regarding gestational age (GA) and/or birth weight (BW) [1].

Exposure to high levels of oxygen saturation has been a well-known risk factor since the 1950s [3]. In middle-income countries, such as Latin America, Asia and Eastern Europe, a 'new epidemic' of ROP is presently seen due to the lack of basic equipment for the administration/monitoring of oxygen and insufficient training [1, 4]. The favourable impact of personal education and improved oxygen administration on the rates of ROP has been presented in several studies [5, 6].

During recent years, poor postnatal weight gain has been acknowledged as a predictor and risk factor for severe ROP [7–10]. Based on these findings, ROP screening surveillance systems such as the WINROP (weight, IGF-I, neonatal, ROP) algorithm have been developed to refine ROP screening [7]. WINROP uses longitudinal weekly weight gain to identify infants at risk of developing ROP type 1 (severe ROP fulfilling treatment criteria) [11]. WINROP was originally developed in a Swedish preterm population and has been validated in another Swedish population with 100% sensitivity and 84.5% specificity [9, 12]. In other countries, the sensitivity and specificity of WINROP have been slightly reduced [13–17]. WINROP was previously validated in infants screened for ROP in 2005–2010 at the neonatal intensive care unit (NICU) at the Hospital Civil de Guadalajara, Mexico [16]. After this prior WINROP study alerted clinicians to the high frequency of ROP treatment, the neonatal care at the NICU was evaluated in greater depth. During the prior study period (2005–2010) preterm infants were exposed to high levels of oxygen saturation, and as a consequence of these findings several implementations and improvements concerning the monitoring and control of oxygen supplementation were initiated in 2011 at the NICU.

The present study was initiated to evaluate the impact of improved neonatal care (monitored and controlled oxygen supplementation) on ROP frequency and WINROP outcome.

Study Population and Methods

Study Population

In this study 151 infants were included, who were born and screened for ROP between November 4, 2012 and March 8, 2014

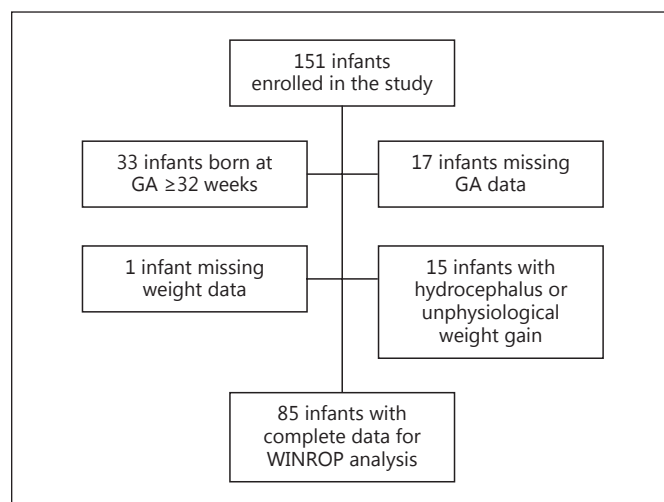


Fig. 1. Flowchart of the WINROP study population, 2012–2014.

at the Hospital Civil de Guadalajara, Mexico. Infants were routinely screened for ROP if they exhibited $BW \leq 1,750$ g and/or were born at $GA \leq 34$ weeks. GA at birth was based on the mother's report of the date of her last menstrual period. Seventeen infants were considered born prematurely; however, the mothers were unable to provide the date of their last menstrual period. Since WINROP requires accurate GA to function, those infants ($n = 17$) were excluded from the WINROP analysis. WINROP was developed for infants with $GA < 32$ weeks; hence infants with higher GA ($n = 33$) were excluded. The weekly weights of all infants throughout their hospital stay were retrieved from hospital records. Infants were excluded if weight data were missing ($n = 1$) or if weight gain was considered non-physiological (not reflecting actual growth) as in hydrocephalus ($n = 15$). Finally, 85 infants met the criteria for WINROP analysis (fig. 1). Small for GA was defined as $BW < 10$ th percentile according to Kramer et al. [18].

ROP Examination and Treatment

ROP screening started after day 21 of life and continued until the retina was fully vascularized or until regression of ROP. Eye examinations were performed weekly according to a routine protocol, and consisted of dilated ocular fundus examinations. International guidelines for the classification of ROP and recommendations for treatment were followed [11, 19].

WINROP Analysis

A person unaware of the ROP outcome retrospectively entered each infant's GA, BW, and weekly weight into the web-based surveillance system WINROP until an alarm was signalled or until a postmenstrual age (PMA) of 33–34 weeks. The WINROP algorithm estimates the differences between the expected safe weekly weight gain and the observed weight gain. An alarm is signalled when the difference exceeds a set limit as a warning that the infant is at risk for ROP type 1, requiring treatment.

Improvements in Monitoring Oxygen Supplementation

The implementations of monitored oxygen supplementation initiated at the NICU in 2011 consisted of improvements in

Table 1. Birth characteristics and ROP development of infants born at GA <32 weeks, screened for ROP at the Hospital Civil de Guadalajara, Mexico, and enrolled in the WINROP studies 2005–2010 and 2012–2014

	WINROP study cohort 2005–2010 (n = 192)	WINROP study cohort 2012–2014 (n = 85)
<i>Birth characteristics</i>		
BW, g	1,430 (1,180–1,510)	1,195 (630–1,760)
GA, weeks+days	31 (28–31)	30+1 (25+3–31+4)
SGA	26 (50)	28 (24)
Male	50 (96)	48 (41)
<i>ROP development</i>		
No ROP	16 (30)	61 (52)
Mild ROP	25 (48)	27 (23)
Severe ROP and AP-ROP	59 (114)	12 (10)
ROP type 1 and treatment	51 (98)	12 (10)

Data are presented as medians (ranges) or % (n). SGA = Small for gestational age, defined as BW <10th percentile by Kramer et al. [18].

Table 2. Birth characteristics and ROP development of infants enrolled in the WINROP study (2012–2014) by cohort and GA week

	Whole cohort (n = 85)	GA 25 (n = 2)	GA 26 (n = 3)	GA 27 (n = 4)	GA 28 (n = 13)	GA 29 (n = 14)	GA 30 (n = 24)	GA 31 (n = 25)
GA, weeks+days	30+0 (27+0–31+5)	–	–	–	–	–	–	–
BW, g	1,160 (630–1,760)	925 (820–1,030)	930 (640–1,020)	1,005 (890–1,210)	1,050 (720–1,530)	1,350 (870–1,670)	1,200 (630–1,640)	1,195 (760–1,760)
Male	48 (41)	50 (1)	100 (3)	75 (3)	62 (8)	29 (4)	50 (12)	40 (10)
No ROP	61 (52)	50 (1)	–	75 (3)	31 (4)	71 (10)	58 (14)	80 (20)
Mild ROP	27 (23)	–	33 (1)	25 (1)	54 (7)	21 (3)	33 (8)	12 (3)
ROP type including AP-ROP ¹	12 (10)	50 (1)	67 (2)	–	15 (2)	7 (1)	8 (2)	8 (2)

Data are presented as medians (ranges) or % (n). ¹ All infants treated.

equipment and education. During the previous WINROP study (2005–2010) oxygen saturation was set to a minimum of 85%; higher levels were allowed and most infants reached 100% oxygen saturation. Oxygen saturation was monitored by pulse oximetry but not on a constant individual basis. In 2011 the target saturation was set to 85–95%; alarms were set to ring when oxygen saturation reached 90–95% and individual infant oxygen pulse oximeters were installed for constant surveillance. Education comprised of a 1- to 2-hour course about the rationale behind the use of oxygen to the neonatologist as well as a 15-min talk to the nurses of each shift, explaining the toxicity of oxygen at high concentrations.

Comparing ROP Frequency and WINROP Outcome with a Prior WINROP Study

The results of this study were compared with results from the prior WINROP study conducted at the Hospital Civil de Guadalajara, Mexico, from 2005 through 2010.

Statistical Analysis

The negative (NPV) and positive predictive values (PPV) were calculated using the sensitivity, specificity, and prevalence of ROP

type 1 for the study group; 95% confidence intervals were calculated. The Mann-Whitney U test was performed to compare ROP frequency within the cohorts.

Ethics Statement

The research ethics committee of the Hospital Civil de Guadalajara approved the study protocol regarding postnatal weight gain and ROP.

Results

ROP Treatment Frequency in All Infants Screened for ROP in the Present Study, 2012–2014

In the present study 151 infants were included. Severe ROP (ROP stage 3–5 or aggressive posterior ROP, AP-ROP) developed in 9.3% (14/151) of infants; all fulfilled the ROP treatment criteria and received treatment. Of the 14 infants receiving ROP treatment, 42.9% (6/14) were male infants. Four infants receiving ROP treatment were

Table 3. WINROP sensitivity, specificity, PPV and NPV in infants born at GA <32 weeks, developing ROP type 1 and receiving ROP treatment during 2005–2010 and 2012–2014

	Alarm status			Sensitivity	Specificity
	alarm	no alarm	total		
<i>Study cohort 2005–2010</i>					
ROP type 1 and treatment	83	15	98	84.7	26.6
No ROP type 1	69	25	94	(75.7–90.9)	(18.2–36.9)
Total	152	40	192		
PPV	54.6				
	(46.3–62.9)				
NPV		62.5			
		(45.8–76.8)			
<i>Study cohort 2012–2014</i>					
ROP type 1 and treatment	8	2	10	80.0	45.3
No ROP type 1	41	34	75	(44.2–96.4)	(33.9–57.2)
Total	49	36	85		
PPV	16.3				
	(7.7–30.2)				
NPV		94.4			
		(80.0–99.0)			

Data are presented as n or % (95% CI).

excluded in the WINROP cohort; 1 infant was born at GA \geq 32 weeks (at GA 32 weeks and 2 days with a BW of 1,540 g), and the other 3 infants were born at GA <32 weeks (2 were excluded due to hydrocephalus and 1 due to uncertain GA). Thirty-three infants screened for ROP were born at GA \geq 32 weeks; no ROP was detected in 70.0% (23/33) and mild ROP (ROP stages 1–2) in 27.3% (9/33). One infant (3.0%, 1/33) developed severe ROP, fulfilled the ROP treatment criteria and received ROP treatment.

Birth Characteristics of Infants in WINROP Analysis in the Present Study, 2012–2014

Eighty-five infants born at GA <32 weeks qualified for WINROP analysis. The birth characteristics of the infants are described in table 1. No ROP was detected in 61.2% (52/85) of infants and mild ROP (ROP stages 1–2) in 27.1% (23/85); severe ROP (ROP stages 3–5 or AP-ROP) developed in 11.8% (10/85). All infants developing severe ROP fulfilled the ROP treatment criteria and received treatment (table 2).

WINROP Identified Infants at Risk of ROP Type 1 with Moderately High Sensitivity in the Present Study, 2012–2014

An alarm was signalled in 58.6% (49/85) of infants. WINROP demonstrated 80.0% sensitivity (8/10) and

45.3% specificity (34/75), with an NPV of 94.4% and a PPV of 16.3% (table 3). Two boys treated for ROP type 1 were not detected by WINROP.

WINROP Sends an Early Alarm in the Present Study, 2012–2014

The median time from birth to alarm was 1 week (range 0–6 weeks). The median PMA at alarm was 31 weeks (range 27–32 weeks).

Results from a Previous WINROP Study, 2005–2010

In the former study, 352 infants were included, of whom 192 infants born at GA <32 weeks met the criteria for WINROP analysis. ROP type 1 developed in 44.0% (155/352) of the infants in the whole cohort, in 51.0% (98/192) of the infants born at GA <32 weeks and in 35.6% (57/160) of the infants born at GA \geq 32 weeks (fig. 2). The most mature infant to develop ROP type 1 and receive treatment was born at GA 35 weeks with a BW of 2,410 g.

Comparison of ROP Treatment Frequency and WINROP Outcomes in 2012–2014 versus 2005–2010

The frequency of ROP treatment was significantly reduced ($p < 0.000$) from 44.0% (155/352) in the 2005–2010 cohort to 9.3% (14/151) in the 2012–2014 cohort. In the previous study 35.6% (57/160) of infants born at GA \geq 32

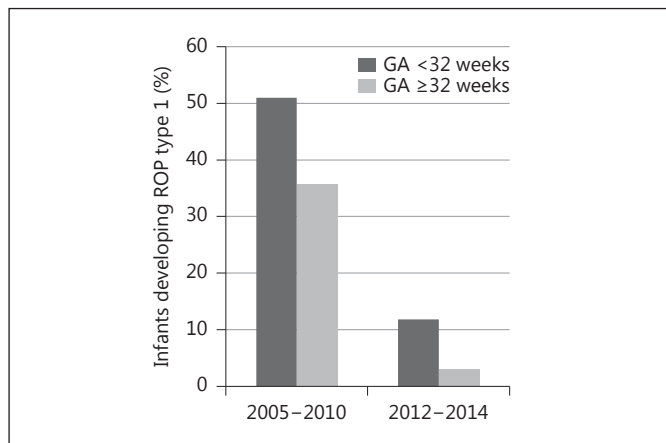


Fig. 2. Percentage of infants developing ROP type 1 during the previous (2005–2010) and the present (2010–2012) study periods.

weeks received ROP treatment, while in the present study only 1 infant (3.0%, 1/33) born at GA \geq 32 weeks required treatment (fig. 2).

WINROP sensitivity for infants born at GA <32 weeks was comparable: 85% in 2005–2010 and 80% in 2012–2014. WINROP specificity improved from 27% in 2005–2010 to 45% in 2012–2014.

Discussion

When validating WINROP in a Mexican cohort born and screened at the Hospital Civil de Guadalajara in 2005–2010, a very high frequency of ROP type 1 fulfilling the treatment criteria was discovered, and alerted clinicians to initiate improvements in neonatal care (monitored and controlled oxygen supplementation). After these improvements the frequency of ROP type 1 was dramatically reduced from 44.0% (2005–2010) to 9.3% (2012–2014). Only 1 infant (3%) born at GA \geq 32 weeks received treatment during the present study period compared to 35.6% during the previous period. We believe that the dramatic reduction of ROP treatment frequency reflects that unrestricted oxygen supplementation is a risk factor with major impact, especially for the more mature infants.

In the present WINROP study WINROP correctly identified 8 of 10 infants born at GA <32 weeks who developed ROP type 1, resulting in 80% sensitivity, similar to the sensitivity of 85% in the previous study. WINROP continues to exhibit lower sensitivity than earlier studies performed in Sweden and North America and there may be several reasons for this. We suspect that inaccurate dating

of GA might contribute to the poorer WINROP outcome in the present study as well as in the previous cohort. In both studies, GA at birth was estimated based on the mother's report of the date of her last menstrual period; in contrast, the WINROP studies in Sweden and North America used routinely performed fetal ultrasound to measure GA. Although fetal ultrasound was performed more frequently during 2012–2014 than during the previous study, its use was not routine and it was performed at different PMAs, making these measurements less useful for gauging GA. The relatively high median BW and large range of BW in the present cohort may also be a reflection of inaccurate GA gauging by the mother. Furthermore, the infants in the Mexican cohort were more mature than in the Swedish cohorts in whom WINROP was developed and validated. No infant born before GA 25 weeks survived to complete ROP screening in the Mexican cohort. Poor living conditions, teenage mothers and the quality of prenatal and postnatal care may affect survival rates. Growth restriction at birth, poor postnatal growth, insufficient nutritional support and neonatal comorbidities such as sepsis, bronchopulmonary dysplasia and necrotizing enterocolitis are risk factors for severe ROP that also depend to some extent on the quality of prenatal and postnatal care [7, 20–25]. Thus, we conclude that WINROP performs less accurately in some populations of preterm infants and should be used with caution where inaccurate dating of GA may be suspected and/or discrepancies in the characteristics of the infants included, from whom WINROP was developed and validated (Sweden and North American).

A limitation of this study is that we have not considered other changes in the general practice of neonatal care during the study periods that may affect ROP frequency. Generally improved neonatal care such as more use of antenatal steroids, gentler resuscitation and better infection control may also be contributing factors to the reduced rates of ROP. Unfortunately, we have no data on these variables and therefore these factors have not been addressed.

In summary, although WINROP may not function as well as desired in the Mexican population of preterm infants, the first WINROP study drew attention to the high frequency of ROP treatment at the Hospital Civil de Guadalajara. Improved control of oxygen supplementation in 2011 resulted in a significant reduction of infants developing ROP type 1 and requiring treatment from 2005–2010 to 2012–2014. Only 1 infant born at GA \geq 32 weeks developed ROP type 1 during the later study period, supporting the hypothesis that uncontrolled oxygen supplementation is the major risk factor for more mature infants. We can only speculate on what consequences this dramatic reduc-

tion in ROP treatment frequency might have for individual infants and from a socioeconomic viewpoint, but we consider the benefits to be substantial. Using WINROP in different populations of preterm infants predicts ROP and also alerts clinicians to outcome differences in study populations, which may initiate improvements in neonatal care.

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Disclosure Statement

WINROP is owned by Premature AB, Uppsala, Sweden. Drs. Hellström, Hård and Löfqvist own shares in a company with financial interest in Premature AB. The other authors declare no conflicts of interest. The sponsors had no role in the study design, the collection, analysis and interpretation of data, the writing of the report or the decision to submit the paper for publication.

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