Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions

Nuria Boronat, MD,[a] Marta Aguar, MD,[a] Denise Rook, MD, PhD,[b] Martin Iriondo, MD,[c] María Brugada, MD,[a] María Cernada, MD, PhD,[d] Antonio Nuñez, MD,[d] Montserrat Izquierdo, MD,[c] Elena Cubells, MD,[d] María Martinez, PSYD, PhD,[d] Anna Parra, MD,[a] Hans van Goudoever, MD, PhD,[e] Máximo Vento, MD, PhD[a,d]

abstract

BACKGROUND AND OBJECTIVES: Stabilization of preterm infants after birth frequently requires oxygen supplementation. At present the optimal initial oxygen inspiratory fraction (Fio_2) for preterm stabilization after birth is still under debate. We aimed to compare neurodevelopmental outcomes of extremely preterm infants at 24 months corrected age randomly assigned to be stabilized after birth with an initial Fio_2 of 0.3 versus 0.6 to 0.65 in 3 academic centers from Spain and the Netherlands.

METHODS: Randomized, controlled, double-blinded, multicenter, international clinical trial enrolling preterm infants <32 weeks' gestation assigned to an initial Fio_2 of 0.3 (Lowox group) or 0.6 to 0.65 (Hiox group). During stabilization, arterial pulse oxygen saturation and heart rate were continuously monitored and Fio_2 was individually titrated to keep infants within recommended ranges. At 24 months, blinded researchers used the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) to assess visual acuity, neurosensory deafness, and language skills.

RESULTS: A total of 253 infants were recruited and 206 (81.4%) completed follow-up. No differences in perinatal characteristics, oxidative stress, or morbidities during the neonatal period were assessed. Mortality at hospital discharge or when follow-up was completed didn't show differences between the groups. No differences regarding Bayley-III scale scores (motor, cognitive, and language composites), neurosensorial handicaps, cerebral palsy, or language skills between groups were found.

CONCLUSIONS: The use of an initial lower (0.3) or higher (0.6–0.65) Fio_2 during stabilization of extremely preterm infants in the delivery room does not influence survival or neurodevelopmental outcomes at 24 months.

[a]Division of Neonatology, University and Polytechnic Hospital La Fe, Valencia, Spain; [b]Division of Neonatology, Sophia Children's Hospital, Erasmus Medical Center, Rotterdam, Netherlands; [c]Division of Neonatology, Hospital Sant Joan de Deu, Barcelona, Spain; [d]Neonatal Research Unit, Health Research Institute La Fe, Valencia, Spain; and [e]Department of Pediatric, Emma Children's Hospital, Academic Medical Center-Amsterdam, VU University Medical Center, Amsterdam, Netherlands

Drs Vento, van Goudoever, Rook, Iriondo, and Aguar conceptualized and designed the study and drafted the initial manuscript; Drs Cernada, Cubells, Nuñez, Izquierdo, and Parra carried out the recruitment, completed the electronic data registry, performed the initial statistical analysis, and reviewed and revised the manuscript; Drs Boronat and Martinez were responsible for the Bayley-III assessment, designed the data collection instruments, coordinated and supervised data collection at 2 of the 3 sites, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

The trials in this article have been registered with the European Clinical Trials Database (https://eudract.ema.europa.eu/) (identifier 2088-005047-42) and with the Netherlands Trial Registry (http://www.trialregister.nl/trialreg/index.asp) (identifier NTR243).

WHAT'S KNOWN ON THIS SUBJECT: Oxygen supplementation in the delivery room to preterm infants is relatively common and should be individually titrated to avoid hyperoxia or hypoxia. Hence, an initial oxygen inspiratory fraction of 0.21 to 0.3 is recommended.

WHAT THIS STUDY ADDS: Follow-up at 24 months corrected age shows no differences in mortality, morbidity, or Bayley Scales of Infant and Toddler Development, Third Edition composite scores for preterm infants <32 weeks' gestation stabalized in the delivery room with initial oxygen respiratory fractions of 0.3 versus 0.60 to 0.65.

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The 2015 International Liaison Committee on Resuscitation (ILCOR) neonatal resuscitation guidelines strongly recommend that preterm infants <35 weeks' gestation should be stabilized at birth with a lower (0.21–0.3) and not higher (>0.65) initial oxygen inspiratory fraction (Fio2).[1] Arterial partial pressure of oxygen increases twofold during fetal to neonatal transition, causing oxidative stress. However, antioxidant defenses are not fully functional until the end of the third trimester,[2] and therefore free radical–associated conditions are more likely in very preterm infants.[3] The use of high oxygen load during resuscitation has been associated with increased and prolonged oxidative stress, bronchopulmonary dysplasia (BPD), and prolonged need for oxygen or mechanical ventilation.[4–8]

Newborn infants achieve arterial pulse oxygen saturation (Spo_2) around 90% at ~5 minutes after birth.[9] In 2010, Dawson et al[10] published a Spo_2 nomogram with preductal values collected in the first 10 minutes after birth from healthy newborn infants' who did not need resuscitation. This database was comprised of 66% term infants and 34% preterm infants, with only 16% <32 weeks' gestation.[10] Of note, preterm infants needed significantly more time to achieve a Spo_2 plateau than term infants.[10] In 2010, the American Heart Association recommended Spo_2 targets between 60% to 65% at 1 minute, 65% to 70% at 2 minutes, 70% to 75% at 3 minutes, 75% to 80% at 4 minutes, 80% to 85% at 5 minutes, and 85% to 95% at 10 minutes.[11] However, these targets were not achieved by a substantial number of preterm infants that were at risk for unnecessary oxygen supplementation.[10] In a recent systematic review and meta-analysis, Saugstad et al[12] compared stabilization of 677 newborn infants ≤32 weeks' gestation resuscitated/stabilized with an initial lower (0.21–0.3) versus higher (0.6–1.0) Fio_2. No differences in the incidence of BPD or intraventricular hemorrhage (IVH) was assessed, but reduced mortality in the lower oxygen group approached significance.[12] No long-term neurocognitive and sensorial follow-up was performed in any of these studies.

We aimed to evaluate neurocognitive and sensorial outcomes of 2 populations of preterm infants randomly assigned to be blindly stabilized with higher (0.60–0.65) or lower (0.30) initial Fio_2s in 3 academic centers in Europe at 24 months after birth.

METHODS

Study Design

Eligible patients were preterm infants <32 weeks' gestation recruited in 2 randomized, controlled, and double-blinded studies[13,14] performed in 2 academic centers in Spain (University and Polytechnic Hospital La Fe and Hospital Sant Joan de Deu), and 1 academic center in the Netherlands (Sophia Children's Hospital, Erasmus Medical Center). Patients were recruited immediately after birth from January 2008 to December 2012. The primary outcome was survival without neurodevelopmental impairment at a corrected age of 2 years. The Spanish study[13] included preterm infants of ≤30 weeks' gestation randomly assigned to resuscitation with an initial Fio_2 of 0.3 (Lowox group) versus 0.6 (Hiox group). The Dutch study[14] included infants <32 weeks' gestation randomly assigned to be resuscitated with an initial Fio_2 of 0.3 (Lowox group) verus 0.65 (Hiox group).

Power calculation required 30 infants per group in the Spanish trial and 90 per group in the Dutch study to find a statistically significant reduction with an α value of 0.05 and a power of 0.80.[13,14] The Spanish study[13] was registered with the European Clinical Trials Database (No. 2088-005047-42) and the Dutch study[14] was registered with the Netherlands Trial Registry (No. NTR243). The ethics committees of the 3 participating hospitals approved the study, and parents of all recruited infants signed informed consent forms.

Population

Inclusion criteria included inborn preterm infants <30 weeks' gestation in the Spanish study[13] and <32 weeks gestation in the Dutch study[14] needing oxygen supplementation for postnatal stabilization and completing follow-up at 24 months corrected age in the participating hospitals. Exclusion criteria included major congenital malformations or chromosome defects identified before or immediately after birth, or loss to/incomplete follow-up.

Methods

Postnatal stabilization was performed according to the ILCOR 2010 guidelines. Initial Fio_2 in both studies was titrated to keep heart rate and Spo_2 within the ranges reflected in the recommendations of the American Heart Association.[11] Resuscitation parameters (Fio_2, respiratory rate, positive pressure, end expiratory pressure, Spo_2, heart rate) were continuously monitored and stored, and biomarkers of oxidative stress were determined in blood and urine at the Research Laboratory of the University and Polytechnic Hospital La Fe and Department of Pediatrics, Obstetrics and Reproductive Medicine (University of Siena, Siena, Italy).[13,14]

Different domains of development were recorded at 24 months corrected age according to standardized protocols as follows:

1. Assessment of growth was recorded (weight, length, and head circumference) relative to

an appropriate growth chart for Spain[15] and the Netherlands.[16]

2. A clinical, specific, and structured neurologic examination was performed and recorded by using standardized forms. Items were grouped in categories (tone, tone patterns, reflexes, movements, abnormal signs, and behavior). Blinded examiners performed patient assessments.
3. Ophthalmologic and audiological assessments were performed by blinded specialists.
4. Certified and blinded psychologists and/or neonatologists performed developmental assessments at 24 months corrected age that included cognitive, language, and motor development using Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).[17] Scales were standardized to a mean (SD) score of 100 points.

Outcomes

Children in each group were compared for cognition, language, and motor function according to the Bayley-III scales[18] as follows: "normal" if the composite score of the respective function scale was greater than or equal to mean – 1 SD; "mildly impaired" if the respective score was less than the mean – 1 SD and greater than or equal to the mean – 2 SD; "moderately impaired" if the score was less than the mean – 2 SD and greater than or equal to the mean – 3 SD; and "severely impaired" if the score was less than mean – 3 SD.

Cerebral palsy (CP) was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture that interfered with or prevented age-appropriate motor activity. CP was classified according to the Gross Motor Function Classification System (GMFCS).[19] The 5 levels of function were: (I) Walks without restrictions; limitations in more advanced gross motor skills; (II) Walks without assistive devices; limitations walking outdoors and in the community; (III) Walks with assistive mobility devices; limitations walking outdoors and in the community; (IV) Self-mobility with limitations; children are transported or use power mobility outdoors and in the community; and (V) Self-mobility is severely limited even with the use of assistive technology.

For sensorial assessment, we included children with severe sensorial impairment. Thus, blindness was defined as the absence of response to fixate or follow a light.[20] Severe hearing loss was defined as permanent hearing loss with no response to amplification.[21]

Finally, summarized outcome was classified as: no disability, mild disability (defined as scores between –1 and –2 SD from the mean in any of the Bayley III scales or mild CP [I and II]), moderate disability (scores between –2 and –3 SD from the mean in any of the Bayley III scales, moderate CP [III]), and severe disability (scores less than the mean –3 SD in any of the Bayley III scales, severe CP [IV and V] or bilateral blindness or deafness).

Statistical Analysis

Data were summarized by using mean (SD) and median (first and third quartile) in the case of continuous variables and with relative and absolute frequencies in the case of categorical variables. The association of Fio_2 with the different items (cognition, language, and motor function) of the Bayley III scales was assessed by using linear regression models to adjust for gestational age and gender. Differences in disability grades were assessed between both groups by using ordinal regression models. Logistic regression was used to assess differences in blindness and deafness risk. *P* values < .05 were considered statistically significant. All statistical analyses were performed by using R Statistical Software, version 3.2.3 (Western Ecology Division, Corvallis, OR).

RESULTS

Figure 1 shows the flow diagram of the patients who were initially included in the study and randomized to lower (Lowox group) or higher (Hiox group) initial Fio_2. In addition, Fig 1 shows patients who died before and after discharge from the hospital. The mortality rate at 24 months corrected age was 8.27% for the Lowox group and 14.04% for the Hiox group. Figure 1 also shows the number of infants lost to follow-up and those who were finally assessed in the Lowox and in the Hiox groups. With respect to gestational age, 55 patients were ≤28 weeks' gestation and 54 patients were >29 weeks' gestation in the Lowox group; 47 patients were ≤28 weeks' gestation and 52 patients were >29 weeks' gestation in the Hiox group.

Table 1 shows the clinical and obstetric baseline characteristics of participating individuals. Table 1 also shows the major complications during hospital stay and mortality at 24 months corrected age. No differences in the incidence of BPD, patent ductus arteriosus, retinopathy of prematurity (ROP), intra-peri-ventricular hemorrhage, or mortality before hospital discharge were detected between both groups. Only 1 infant from the Spanish study[13] died after hospital discharge. Of the survivors, 15 infants in the Lowox group and 5 infants in the Hiox group were lost to follow-up.

Table 2 shows the baseline characteristics at follow-up. The median corrected age and children's growth charts were similar in both groups.

Table 3 shows the Bayley-III scoring results. Of the 207 patients eligible for assessment in the follow-up clinic, 170 (81.7%) completed the cognitive scale, 144 (69.2%) completed the motor scale, and 142 (68.2%) completed the language evaluation of the Bayley-III test. A total of 32 patients (15.4%) missed the appointment and, of those who attended, 6 patients (2.9%) did not perform the Bayley-III evaluation because of lack of cooperation. Of the 38 patients who did not attend or perform the follow-up assessment, 34 (16.4% of the eligible [*n* = 207] and 89.5% of the nonevaluated patients) were immigrants with low socioeconomic and educational status. Table 3 shows the mean (SD) for cognitive, motor, and language scoring for the entire population. In addition, we also performed a subanalysis of the results taking into consideration gestational age and gender. There were no statistical differences between groups for cognitive scale scores by gestational age (odds ratio [OR], 0.46; 95% confidence interval [CI], −0.52 to 1.46) or sex (1.91; 95% CI, −2.25 to 6.07; *P* = .37), for motor scale by gestational age (0.36; 95% CI, −0.69 to 1.42) or sex (1.31; 95% CI, −3.02 to 5.63; *P* = .55), or for language evaluation by gestational age (1.06; 95% CI, −0.15 to 2.27) or sex (-4.01; 95% CI, −9.13 to 1.10; *P* = .12).

As shown in Table 4, according to the results of the Bayley-III scales, patients were classified into 4 severity categories in each group: no disability and mildly, moderately or, severely disabled (see Methods). No differences between groups or severity categories were found (cognitive: OR, 1.05; 95% CI, 0.34–3.20; motor: OR, 1.69; 95% CI, 0.40–8.49; and language: OR, 1.58; 95% CI, 0.70–3.59). Detailed description of results by category is provided in Table 4. Figure 2, in addition, shows the composite scores' differences for mean Bayley-III composites (cognitive, motor, and language).

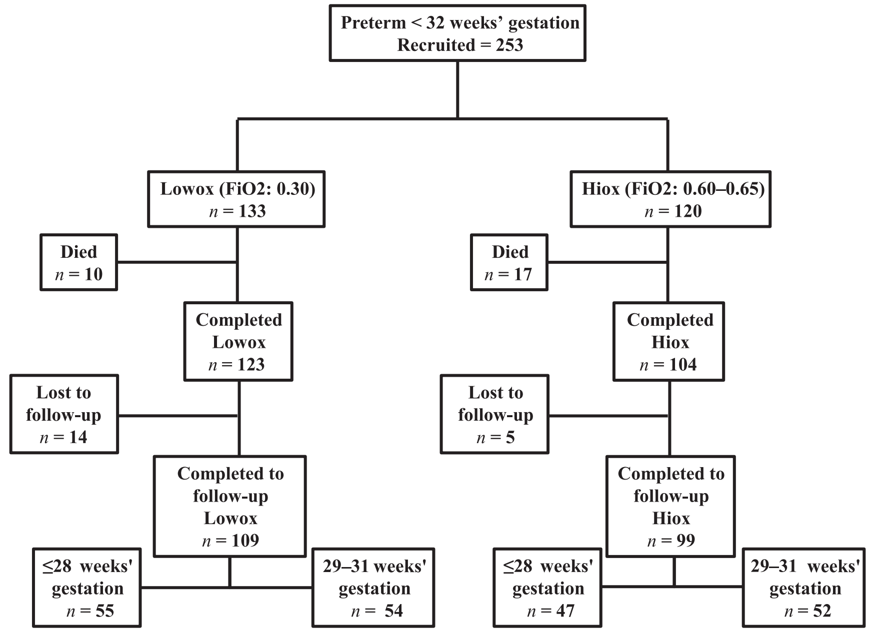

FIGURE 1
Flow diagram showing patients recruited and randomized to the Lowox group (initial Fio_2, 0.30) or the Hiox group (Fio_2, 0.60–0.65), patients who died or were lost to follow-up, and patients who finally completed follow-up classified by gestational age.

Cerebral Palsy and Sensory Disabilities

Table 5 shows the incidence of cerebral palsy (CP) for both groups (Lowox and Hiox). CP was present in 4 patients (3.7%) in the Lowox group, all of whom were classified as mild by using the GMFCS. Hence, 3 patients pertained to group 1 (7.4%), and 1 patient to group 2 (2.6%). In the Hiox group, 4 patients (4.1%) were diagnosed with CP and classified each one for every group. As shown in Table 5, neurosensorial evaluation revealed that 1 patient in the Hiox group was impaired with blindness (1%) and 1 patient in the Lowox group was impaired with deafness (1%).

Overall Rate of Disabilities

The overall rate of disabilities (Table 6) included performance

TABLE 1 Basic Clinical and Obstetric Characteristics and Complications During the Neonatal Period of Preterm Infants Randomly Assigned to an Initial Fio_2 of 0.3 (Lowox Group) versus 0.60 to 0.65 (Hiox Group) and Mortality at 24 Months Corrected Age

Parameter	Lowox (*n* = 133)	Hiox (*n* = 120)
Girl, *n* (%)	69 (51.8)	58 (48.3)
GA (wk), median (IQR)	28 (24–32)	27 (23–31)
Birth weight (g), median (IQR)	944 (720–1280)	1040 (755–1368)
Umbilical cord pH, median (IQR)	7.29 (7.25–7.33)	7.28 (7.23–7.31)
Full antenatal steroids, *n* (%)	133 (100)	120 (100)
Vaginal/cesarean delivery, *n*	43/90	44/76
Chorioamnionitis, *n* (%)	25 (18.8)	22 (18.3)
BPD, *n* (%)	33 (24.8)	20 (16.6)
PDA, *n* (%)	58 (43.6)	43 (35.8)
ROP (≥ grade 2)	10 (7.5)	6 (5.0)
NEC (≥ grade 2)	6 (4.5)	4 (3.3)
IVH (grades 3/4)	19 (14.3)	18 (15.0)
Mortality at 24 mo corrected age, *n* (%)	11 (8.27)	17 (14.04)

GA, gestational age; IQR, interquartile range; NEC, necrotizing enterocolitis; PDA, persistent ductus arteriosus.

TABLE 2 Baseline Characteristics of Very Preterm Infants Resuscitated With an Initial Fio_2 of 0.3 (Lowox Group) versus 0.6 to 0.65 (Hiox Group) at 24 Months Corrected Age

Variable	Lowox (*n* = 108)	Hiox (*n* = 99)
Weight (kg)	11.5 (1.6)	11.5 (1.4)
Length (cm)	85.6 (3.9)	86.4 (3.6)
Head circumference (cm)	48.0 (1.9)	48.2 (1.6)
Corrected age at follow-up (mo)	24.7 (1.5)	24.5 (1.2)

Results are expressed as means (SD).

TABLE 3 Bayley-III Scoring in Very Preterm Infants Initially Resuscitated With an Fio_2 of 0.3 (Lowox Group) versus 0.6 to 0.65 (Hiox Group) at 24 Months Corrected Age

Variable	Lowox Total	Hiox Total	*P*
Cognitive composite (*N* = 170)	96.8 (17.6)	98.9 (17.4)	.37
Cognitive SD	−0.014 (0.9)	0.01 (0.9)	.12
Sex differences			.35
Gestational age differences			
Motor composite (*N* = 144)	98.8 (18.2)	100.2 (16.7)	.55
Gross motor score	10.8 (2.8)	11.2 (2.9)	.51
Fine motor score	8.9 (2.7)	8.89 (2.7)	.49
Motor SD	0 (0.9)	0.1 (0.8)	
Sex differences			
Gestational age differences			
Language composite (*N* = 142)	92.6 (19.5)	88.5 (18.2)	.12
Language SD	−0.4 (1.1)	−0.67 (1.0)	.66
Sex differences			.11
Gestational age differences			

Results are expressed as means (SD). Comparisons have been made for all the patients recruited and for the subgroup of infants <29 weeks' gestation.

TABLE 4 Disability Categories According to the Results of the Bayley-III Scales for Preterm Infants Resuscitated With an Initial Fio_2 of 0.3 (Lowox Group) versus 0.60 to 0.65 (Hiox Group) at 24 Months Corrected Age

Variable	Lowox Total, *n* (%)	Hiox Total, *n* (%)	OR (95% CI)	*P*
Cognitive			1.05 (0.34–3.20)	.93
No disability	81 (92.0)	75 (91.5)		
Mild	4 (4.5)	6 (7.3)		
Moderate	2 (2.3)	1 (1.2)		
Severe	1 (1.1)	0 (0)		
Motor			1.69 (0.40–8.49)	.48
No disability	70 (95.9)	66 (93.0)		
Mild	0 (0)	3 (4.2)		
Moderate	2 (2.7)	1 (1.4)		
Severe	1 (1.4)	1 (1.4)		
Language			1.58 (0.70–3.59)	.27
No disability	62 (82.7)	50 (74.6)		
Mild	9 (12.0)	13 (19.4)		
Moderate	3 (4.0)	4 (6.0)		
Severe	1 (1.3)	0 (0)		

Comparison have been made for all of the patients recruited (total) and for the subgroup of infants <29 weeks' gestation.

on the Bayley-III assessment, CP, and neurosensorial disability, as described above. Of the 208 patients evaluated, 67 children (75.3%) in the Lowox group were classified as normal (no disability) versus 61 patients (71.8%) in the Hiox group. Rates of moderate to severe disability were also similar between groups (8.99% in Lowox versus 9.41% in Hiox group). No statistical differences between groups (OR, 1.17; 95% CI, 0.60–2.30).

DISCUSSION

Survival of extremely preterm infants has improved in recent years; however, both neurodevelopmental and/or sensorial impairment still affect a substantial number of survivors.[22] Term infants resuscitated with 100% oxygen exhibited prolonged oxidative stress after birth and had increased mortality.[4,23] Moreover, epidemiologic studies have shown that exposure to oxygen even for brief periods of time immediately after birth is associated with an increased incidence of childhood cancer.[24] The use of high oxygen concentrations in preterm infants has been associated with severe neonatal conditions, such as BPD, ROP and IVH.[2,3,5–8] Furthermore, preterm infants stabilized with higher oxygen concentrations (Fio_2 > 0.9) have higher levels of oxidative stress biomarkers and BPD.[5–8]

To date, the optimal initial Fio_2 to stabilize preterm infants in the delivery room is still under debate.[3,12,25–27] Although most experts agree that individually titrating Fio_2 to achieve targeted Spo_2 according to saturation ranges is the best applicable approach, it is not clear if the initial Fio_2 should be set at a higher (>50%) or lower (<50%) oxygen concentration. In this scenario, ILCOR 2015 guidelines strongly recommend the use of an initial low Fio_2 (0.21–0.3) for all preterm infants <35 weeks' gestation.[1] However, this recommendation has been questioned based on recently published information.[28,29] Oei et al[30] presented results of the largest randomized controlled trial (RCT) completed to date, which examined the effects of resuscitation with room air versus 100% oxygen in 289 preterm infants <32 weeks' gestation. Mortality in the subgroup of infants <29 weeks' gestation was 16.2% in the air group and 6% in the 100% oxygen group. This difference, although statistically marginal, emphasized the urgent need for larger RCTs to examine

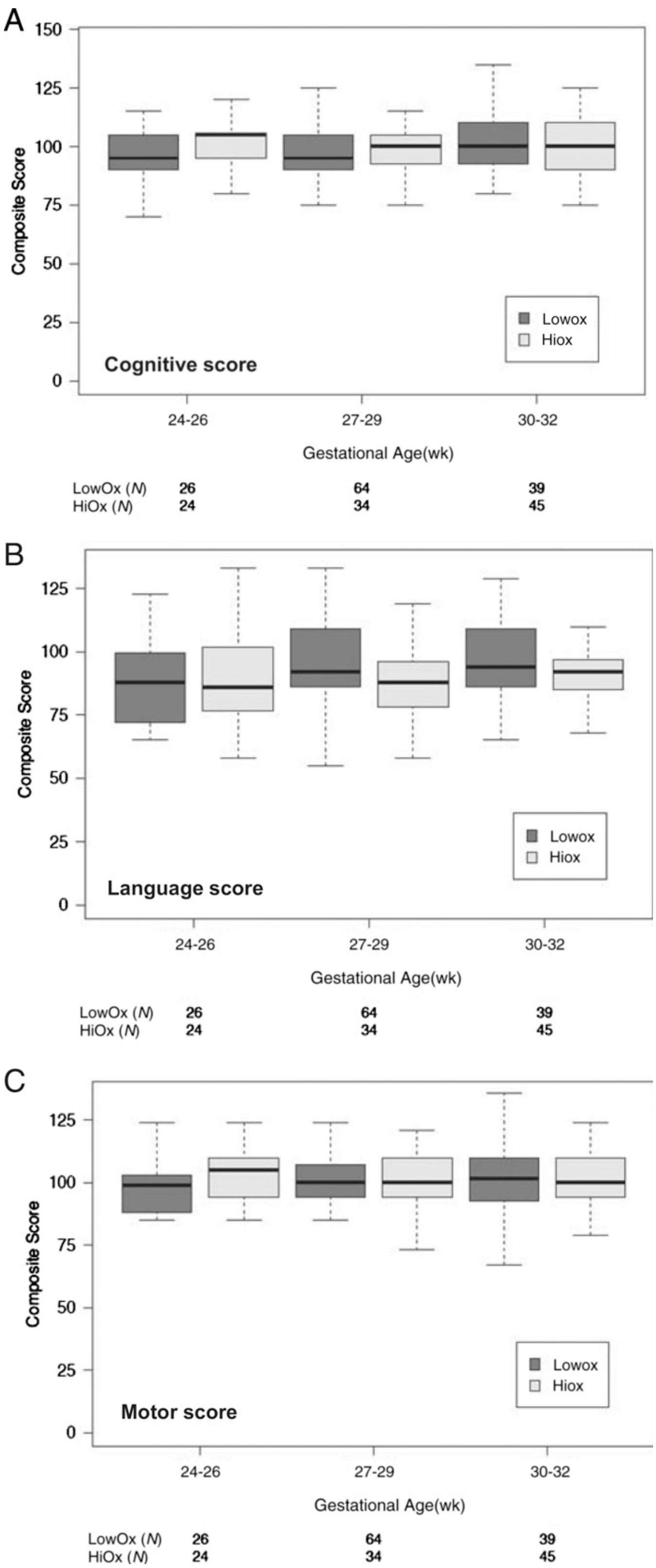

FIGURE 2
Bayley-III composite scores at 24 months corrected age in premature infants who were initially stabilized with an FiO_2 of 0.3 (Lowox group) or 0.60-0.65 (Hiox group). A, Cognitive; B, language; and C, motor.

this question.[30] In addition, the Canadian Neonatal Network, in a retrospective cohort study, compared major outcomes of infants ≤27 weeks' gestation before and after 2006 when the policy regarding the initial FiO_2 for preterm infants in the delivery room was changed from 100% to <100% oxygen.[31] Adjusted OR for the primary outcome of severe neurologic injury or death was higher in the lower oxygen group and in those resuscitated with air when compared with 100% oxygen. Although no data about oxygen exposure for each individual infant were available, the investigators cautioned against a policy of initial stabilization of very preterm infants with lower oxygen that could imply a higher risk of severe neurologic injury or death compared with starting with 100% oxygen.[31]

Our study has evaluated for the first time neurodevelopmental and sensorial outcome of very preterm infants resuscitated with lower versus higher oxygen at 24 months corrected age. Infants in the Lowox group (initial FiO_2, 0.3) received significantly less oxygen in the first few minutes of life compared with those in the HiOx group (initial FiO_2, 0.6 to 0.65). As shown by Rook et al,[14] differences in FiO_2 were significant for the first 6 minutes after birth. However, we have found no statistical differences for survival and/or major morbidities in the neonatal period independent of the initial FiO_2. Thus, mortality was 8.27% for the lower oxygen and 14.04% for the higher oxygen group. We also did not find differences in mortality when comparing our rates with those described by Oei et al[30] for infants receiving air or pure oxygen.

In spite of the differences in oxygenation during the first minutes after birth, follow-up evaluation at 24 months corrected age did not show significant differences in Bayley-III scores in 88.6% of

TABLE 5 CP or Neurosensorial Disabilities in Preterm Infants Resuscitated With an Initial Fio_2 of 0.3 (Lowox Group) versus 0.6 to 0.65 (Hiox Groups) at 24 Months Corrected Age

Variable	Lowox Total, *n* (%)	Hiox Total, *n* (%)	OR (95% CI)	*P*
Cerebral Palsy			1.12 (0.26–4.84)	.88
No	105 (96.3)	94 (95.9)		
Any	4 (3.7)	4 (4.1)		
GMFCS			1.29 (0.30–5.58)	.72
I	3 (7.9)	1 (3.4)		
II	1 (2.6)	1 (3.4)		
III	0 (0)	1 (3.4)		
IV	0 (0)	1 (3.4)		
Visual impairment			3.37 (0.19–Inf)	.46
No	109 (100)	97 (99)		
Blindness	0 (0)	1 (1)		
Hearing impairment			0.38 (0–6.81)	.56
No	112 (99.1)	98 (100)		
Deafness	1 (0.9)	0 (0)		

Comparisons have been made for all of the patients recruited (total) and for the subgroup of infants <29 weeks' gestation.

TABLE 6 Overall Rate of Disabilities in Preterm Infants Resuscitated With an Initial Fio_2 of 0.3 (Lowox Group) versus 0.6 to 0.65 (Hiox Group) at 24 Months Corrected Age

Variable	Lowox Total, *n* (%)	Hiox Total, *n* (%)	OR (95% CI)	*P*
Disability			1.17 (0.60–2.30)	.64
No disability	67 (75.3)	61 (71.8)		
Mild	14 (15.7)	16 (18.8)		
Moderate	6 (6.7)	7 (8.2)		
Severe	2 (2.3)	1 (1.2)		

patients in the Lowox and in 95.0% of patients in the Hiox group. At follow-up, 73.6% of patients were nondisabled (75.3% in the Lowox group and 71.8% in Hiox group). Disabilities detected were mild in both groups (15%–20%) and the combined prevalence of moderate and severe disabilities was 9% in the Lowox group and 9.4% in the Hiox group, which is comparable to similar published studies.[32–38] The rate of CP (3.8%) was not different between groups. Of note, subgroup analysis of infants according to gestational age did not find significant differences between groups in mortality, as opposed to Oei et al,[30] or in sensorial or neurocognitive impairment.

Although the strengths of this study rely on the inclusion of randomized and blinded enrollment and multidisciplinary monitoring of patients with a relevant follow-up rate (total follow-up rate, 81.9%), there are some limitations that should be underscored.

Our patients were resuscitated with an initial Fio_2 of 0.3 versus 0.6–0.65. This difference in oxygen load didn't cause significant differences in mortality, biochemical results,[13,14] short- and long-term outcomes (Table 1), and neurocognitive and sensorial assessment (Tables 2, 3, 4, 5, and 6). However, long-term results in preterm infants initially resuscitated with an Fio_2 of 1.0 have not yet been performed. The use of pure oxygen provides a substantially greater total oxygen load at the end of resuscitation, which has been associated with increased levels of oxidative stress biomarkers, more prolonged use of oxygen, and/or BPD.[7,13,14,39,40]

Another limitation relates to the fact that 20% to 30% of patients did not come to the clinic to perform follow-up assessment or were not able to complete it. It has been shown that fidelity to appointments for follow-up greatly correlates with socioeconomic inequalities.[41] A considerable number of infants were from immigrant families with low socioeconomic and educational status and frequent changes of residence. These factors may explain losses to follow-up.

To our knowledge, this is the first study that has compared neurocognitive and sensorial outcomes at 2 years corrected age in preterm infants stabilized with higher or lower initial Fio_2. Both studies were randomized, controlled, and blinded trials, thus achieving a high grading of evidence. In addition, long-term follow-up of these patients, including academic, behavioral, and psychological assessment, is ongoing at all of the participating centers. We conclude that there are no differences in neurocognitive and sensorial outcomes at 24 months corrected age in preterm infants resuscitated with an initial Fio_2 of 0.3 versus 0.6 to 0.65. Powered RCTs with saturation targets at specific time points for extremely preterm infants are required to assess if there are differences in mortality and/or long-term outcomes.

ABBREVIATIONS

Bayley-III: Bayley Scales of Infant and Toddler Development, Third Edition
BPD: bronchopulmonary dysplasia
CI: confidence interval
CP: cerebral palsy
Fio_2: oxygen inspiratory fraction
GMFCS: Gross Motor Function Classification System
ILCOR: International Liaison Committee on Resuscitation
IVH: intraventricular hemorrhage
OR: odds ratio
RCT: randomized controlled trial
ROP: retinopathy of prematurity
Spo_2: arterial pulse oxygen saturation

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Address correspondence to Máximo Vento, MD, PhD, Division of Neonatology, Health Research Institute La Fe, University and Polytechnic Hospital La Fe, Avenida Fernando Abril Martorell 101, 46026 Valencia, Spain. E-mail: maximo.vento@uv.es

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REFERENCES

1. Perlman JM, Wyllie J, Kattwinkel J, et al; Neonatal Resuscitation Chapter Collaborators. Part 7: Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2015;132(16 suppl 1):S204–S241
2. Vento M, Aguar M, Escobar J, et al. Antenatal steroids and antioxidant enzyme activity in preterm infants: influence of gender and timing. *Antioxid Redox Signal*. 2009;11(12):2945–2955
3. Vento M. Oxygen supplementation in the neonatal period: changing the paradigm. *Neonatology*. 2014;105(4):323–331
4. Vento M, Asensi M, Sastre J, García-Sala F, Pallardó FV, Viña J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. *Pediatrics*. 2001;107(4):642–647
5. Ezaki S, Suzuki K, Kurishima C, et al. Resuscitation of preterm infants with reduced oxygen results in less oxidative stress than resuscitation with 100% oxygen. *J Clin Biochem Nutr*. 2009;44(1):111–118
6. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics*. 2009;124(3). Available at: www.pediatrics.org/cgi/content/full/124/3/e439
7. Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of preterm neonates with limited versus high oxygen strategy. *Pediatrics*. 2013;132(6). Available at: www.pediatrics.org/cgi/content/full/132/6/e1488
8. Tataranno ML, Oei JL, Perrone S, et al. Resuscitating preterm infants with 100% oxygen is associated with higher oxidative stress than room air. *Acta Paediatr*. 2015;104(8):759–765
9. Finer N, Leone T. Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. *Pediatr Res*. 2009;65(4):375–380
10. Dawson JA, Kamlin CO, Vento M, et al. Defining the reference range for oxygen saturation for infants after birth. *Pediatrics*. 2010;125(6). Available at: www.pediatrics.org/cgi/content/full/125/6/e1340
11. Kattwinkel J, Perlman JM, Aziz K, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S909–S919
12. Saugstad OD, Aune D, Aguar M, Kapadia V, Finer N, Vento M. Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤32 weeks. *Acta Paediatr*. 2014;103(7):744–751
13. Aguar M, Cubells E, Escobar J, et al. Preterm babies randomly assigned to be blindly resuscitated with higher (60%) vs. lower (30%) initial fio2: effects on oxidative stress and mortality. In: 2014 Pediatric Academic Societies/Asian Society for Pediatric Research Joint Meeting; May 3–6, 2014; Vancouver, British Columbia, Canada; 3843.540
14. Rook D, Schierbeek H, Vento M, et al. Resuscitation of preterm infants with different inspired oxygen fractions. *J Pediatr*. 2014;164(6):1322–6.e3
15. Carrascosa Lezcano A, Fernández García JM, Fernández Ramos C, et al; Grupo Colaborador Español. [Spanish cross-sectional growth study 2008. Part II. Height, weight and body mass index values from birth to adulthood]. *An Pediatr (Barc)*. 2008;68(6):552–569
16. Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res*. 2000;47(3):316–323
17. Bayley N. *Bayley Scales of Infant and Toddler Development*, 3rd ed. San Antonio, TX: Harcourt Assessment; 2006
18. Spencer-Smith MM, Spittle AJ, Lee KJ, Doyle LW, Anderson PJ. Bayley-III Cognitive and Language Scales in Preterm Children. *Pediatrics*. 2015;135(5). Available at: www.pediatrics.org/cgi/content/full/135/5/e1258

19. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214–223

20. Nyong'o OL, Del Monte MA. Childhood visual impairment: normal and abnormal visual function in the context of developmental disability. *Pediatr Clin North Am*. 2008;55(6):1403–1415

21. Smith RJ, Bale JF Jr, White KR. Sensorineural hearing loss in children. *Lancet*. 2005;365(9462):879–890

22. García-Muñoz Rodrigo F, Díez Recinos AL, García-Alix Pérez A, Figueras Aloy J, Vento Torres M. Changes in perinatal care and outcomes in newborns at the limit of viability in Spain: the EPI-SEN Study [published correction appears in *Neonatology* 2015;107(3):224]. *Neonatology*. 2015;107(2):120–129

23. Saugstad OD, Ramji S, Soll RF, Vento M. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. *Neonatology*. 2008;94(3):176–182

24. Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA. Childhood cancer following neonatal oxygen supplementation. *J Pediatr*. 2005;147(1):27–31

25. Brown JV, Moe-Byrne T, Harden M, McGuire W. Lower versus higher oxygen concentration for delivery room stabilisation of preterm neonates: systematic review. *PLoS One*. 2012;7(12):e52033

26. Goldsmith JP, Kattwinkel J. The role of oxygen in the delivery room. *Clin Perinatol*. 2012;39(4):803–815

27. Dawson JA, Vento M, Finer NN, et al. Managing oxygen therapy during delivery room stabilization of preterm infants. *J Pediatr*. 2012;160(1):158–161

28. Vento M, Schmölzer G, Cheung PY, et al. What initial oxygen is best for preterm infants in the delivery room?-A response to the 2015 neonatal resuscitation guidelines. *Resuscitation*. 2016;101:e7–e8

29. Saugstad OD, Robertson NJ, Vento M. A critical review of the 2015 International Liaison Committee on Resuscitation treatment recommendations for resuscitating the newly born infant. *Acta Paediatr*. 2016;105(5):442–444

30. Oei JL, Wright IM, Craven P, Saugstad OD, Coates E, Tarnow-Mordi WO. Targeted oxygen in the resuscitation of preterm infants and their developmental outcomes (TO2RPIDO): A randomized controlled trial (RCT). In: *Proceedings of the 2015 Pediatric Academic Societies (PAS) Annual Meeting*; April 25–28, 2015; San Diego, CA

31. Rabi Y, Lodha A, Soraisham A, Singhal N, Barrington K, Shah PS. Outcomes of preterm infants following the introduction of room air resuscitation. *Resuscitation*. 2015;96:252–259

32. Doyle LW, Roberts G, Anderson PJ; Victorian Infant Collaborative Study Group. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. *J Pediatr*. 2010;156(1):49–53.e1

33. Hintz SR, Kendrick DE, Wilson-Costello DE, et al; NICHD Neonatal Research Network. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. *Pediatrics*. 2011;127(1):62–70

34. Claas MJ, Bruinse HW, Koopman C, van Haastert IC, Peelen LM, de Vries LS. Two-year neurodevelopmental outcome of preterm born children ≤ 750 g at birth. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(3):F169–F177

35. Mercier CE, Dunn MS, Ferrelli KR, Howard DB, Soll RF; Vermont Oxford Network ELBW Infant Follow-Up Study Group. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998-2003. *Neonatology*. 2010;97(4):329–338

36. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ*. 2012;345:e7961

37. Serenius F, Källén K, Blennow M, et al; EXPRESS Group. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA*. 2013;309(17):1810–1820

38. Hirvonen M, Ojala R, Korhonen P, et al. Cerebral palsy among children born moderately and late preterm. *Pediatrics*. 2014;134(6). Available at: www.pediatrics.org/cgi/content/full/134/6/e1584

39. Vento M, Asensi M, Sastre J, Lloret A, García-Sala F, Viña J. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr*. 2003;142(3):240–246

40. Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics*. 2008;121(6):1083–1089

41. Howe LD, Tilling K, Galobardes B, Lawlor DA. Loss to follow-up in cohort studies: bias in estimates of socioeconomic inequalities. *Epidemiology*. 2013;24(1):1–9

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