Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants

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Objective To determine the efficacy and safety of automated adjustment of the fraction of inspired oxygen (FiO_2) in maintaining arterial oxygen saturation (SpO_2) within a higher (91%-95%) and a lower (89%-93%) target range in preterm infants.

Study design Eighty preterm infants (gestational age [median]: 26 weeks, age [median] 18 days) on noninvasive (n = 50) and invasive (n = 30) respiratory support with supplemental oxygen, were first randomized to one of the SpO_2 target ranges and then treated with automated FiO_2 (A-FiO_2) and manual FiO_2 (M-FiO_2) oxygen control for 24 hours each, in random sequence.

Results The percent time within the target range was higher during A-FiO_2 compared with M-FiO_2 control. This effect was more pronounced in the lower SpO_2 target range (62 ± 17% vs 54 ± 16%, $P < .001$) than in the higher SpO_2 target range (62 ± 17% vs 58 ± 15%, $P < .001$). The percent time spent below the target or in hypoxemia (SpO_2 <80%) was consistently reduced during A-FiO_2, independent of the target range. The time spent above the target range or at extreme hyperoxemia (SpO_2 >98%) was only reduced during A-FiO_2 when targeting the lower SpO_2 range (89%-93%). These outcomes did not differ between infants on noninvasive and invasive respiratory support. Manual adjustments were significantly reduced during A-FiO_2 control.

Conclusions A-FiO_2 control improved SpO_2 targeting across different SpO_2 ranges and reduced hypoxemia in preterm infants on noninvasive and invasive respiratory support. *(J Pediatr 2015;167:545-50)*.

Trial registration ISRCTN 56626482.

Extremely preterm infants often require supplemental oxygen to ensure adequate oxygen delivery to the tissues. The fraction of inspired oxygen (FiO_2) is usually titrated on the basis of the arterial oxygen saturation (SpO_2) measured with pulse oximetry. In addition to targeting normoxemia, avoiding both hypoxemia and hyperoxemia are important goals during oxygen supplementation, as these conditions are associated with, respectively, an increased risk of mortality and retinopathy of prematurity.[1,2] However, SpO_2 control during routine care by manually adjusting the FiO_2 is a challenging task that is often not successful. In fact, infants receiving supplemental oxygen spend approximately 50% of the time within, 30% of the time above, and 20% of the time below the intended SpO_2 range.[3,4]

With the purpose of improving oxygen targeting, an algorithm for automated adjustments of FiO_2 in response to changes in SpO_2 was developed and incorporated into a standard neonatal ventilator. This algorithm improves maintenance of oxygenation within an intended SpO_2 range compared with routine and even dedicated manual FiO_2 (M-FiO_2) control.[5-7] Studies have focused on oxygen dependent, mechanically ventilated infants with frequent episodes of hypoxemia using a single and relatively wide SpO_2 target range.

Our objective was to assess the efficacy of automated FiO_2 (A-FiO_2) control in targeting 2 different, relatively narrow SpO_2 target ranges in more stable, oxygen-dependent infants on both invasive and noninvasive respiratory support. We hypothesized that A-FiO_2 control would increase the time within the SpO_2 target range and reduce both hypoxemia and hyperoxemia compared with

A-FiO_2	Automated FiO_2
FiO_2	Fraction of inspired oxygen
M-FiO_2	Manual FiO_2
SpO_2	Arterial oxygen saturation

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M-FiO_2 control by the clinical staff during routine care, independent of the SpO_2 target range and mode of respiratory support.

Methods

This study was designed as a multicenter, randomized, cross-over clinical trial in 8 European and 1 Canadian level III and IV neonatal intensive care units. The study was approved by institutional review boards in each institution, with written parental informed consent.

Oxygen-dependent preterm infants born with a gestational age <33 weeks and weighing between 0.4 and 4 kg at the time of the study, receiving invasive mechanical ventilation or noninvasive respiratory support were considered eligible for the study. Infants with major congenital anomalies, hemodynamic instability requiring vasopressor treatment or inhaled nitric oxide, or culture proven sepsis within 72 hours prior of enrollment were excluded.

The study consisted of 2 consecutive periods where each enrolled infant was treated with both A-FiO_2 and M-FiO_2 control for 24 hours each. Randomization was done in 2 levels, using sequentially numbered opaque sealed envelopes. First, infants were randomized to 1 of 2 SpO_2 target ranges (89%-93% or 91%-95%), which was maintained for the entire 48-hour study period. Second, infants were randomly assigned to 1 of 2 sequences (A-FiO_2/M-FiO_2 or M-FiO_2/A-FiO_2). The randomization procedure was separate for infants on noninvasive support and those mechanically ventilated and in blocks by center.

Respiratory support was with ventilators (Avea; CareFusion, Yorba Linda, California) with a built-in A-FiO_2 adjustment function. A neonatal pulse oximeter (Radical; Masimo Corporation, Irvine, California) integrated in the ventilator was used to measure SpO_2 (normal sensitivity, averaging time 8 seconds) during both A-FiO_2 and M-FiO_2. This system is approved for clinical use in the countries where the study was conducted.

A-FiO_2 Control

At the start, the A-FiO_2 function adopts the current FiO_2 as the baseline-FiO_2. This is the FiO_2 necessary to keep SpO_2 within the intended target range during relatively stable conditions. Over time, the baseline FiO_2 is slowly and automatically updated, reflecting the trend of the FiO_2 needed to maintain the SpO_2 within the target range. The actual delivered FiO_2 is automatically adjusted (up to once every second) in response to changes in SpO_2. The magnitude and rate of FiO_2 changes are determined by the difference between the actual SpO_2 and the target range, the time outside the range, the SpO_2 trend, and the baseline FiO_2. If deemed clinically necessary, the nursing staff could increase the delivered A-FiO_2 manually by 0.20 for a maximum time of 2 minutes.

SpO_2 alarms were set at 1% below and 1% above the target range with a delay time of 30 seconds. The high SpO_2 alarm could be disabled if the FiO_2 reached 0.21 and the SpO_2 remained within or above the assigned target range for more than 30 minutes. Under these circumstances, the low FiO_2 alarm could also be disabled. If FiO_2 increased again, both alarms were reinstituted. The high FiO_2 alarm was set at 1.0 and, in addition, an alarm was activated when the baseline FiO_2 increased by 0.30. In the event of poor SpO_2 signal quality or signal loss, the automated system assumed a fail-safe state, and the FiO_2 was set at the highest of the following: the current baseline-FiO_2, the median FiO_2 of the preceding 15 seconds, and the backup-FiO_2 level set by the operator.

M-FiO_2 Control

Manual adjustments of the FiO_2 to maintain the SpO_2 target range were done as part of routine care by the attending nursing staff. To limit personnel or center-dependent variability study specific guidelines for M-FiO_2 adjustments were given to the clinical staff (**Appendix**; available at www.jpeds.com). SpO_2 alarm settings were the same as those for the A-FiO_2 period.

Exit Criteria

Infants were to exit the study if they met any of the following criteria: withdrawal of parental consent, transition from invasive to noninvasive respiratory support or vice versa during the study, meeting one of the exclusion criteria during the study period, the attending physician decided it was in the best interest of the patient to exit the study, discharge, transfer to another hospital, or death.

Data and Safety Monitoring

A 3-member independent data and safety monitoring board reviewed the study at 50% enrollment and could recommend termination if adverse events suggested undue risk, the main endpoint was significantly worse during A-FiO_2, futility was demonstrated, or protocol violations compromised scientific validity. A clinical monitor oversaw compliance with the protocol and human subject research and regulatory rules. The monitor reviewed the uploaded data from each individual patient and provided periodic feedback to the sites on protocol compliance and achievement of the SpO_2 targets during manual control. Protocol deviations monitored during the study included but were not limited to inappropriate setting of the A-FiO_2 function, SpO_2 targets, monitoring alarms, or incorrect sequence of FiO_2 control mode.

Data Collection and Analyses

Demographic data including gestational age, birth weight, sex, postnatal age, and weight were collected at time of enrollment. Ventilator settings and monitored variables including SpO_2, FiO_2, pulse rate, and alarms were recorded every 5 seconds by an electronic data logger. In addition, the nurse:patient and patient care procedures that could impact SpO_2 stability were documented. The electronic data were analyzed off-line for each infant for both 24-hour periods using study dedicated software without operator intervention.

The primary endpoint was defined as the proportion of time with SpO_2 within the assigned target range plus the