Randomized controlled trial of low vs high oxygen during neonatal anesthesia: Oxygenation, feasibility, and oxidative stress

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**Abstract**

**Background:** To reduce risk for intermittent hypoxia a high fraction of inspired oxygen is routinely used during anesthesia induction. This differs from the cautious dosing of oxygen during neonatal resuscitation and intensive care and may result in significant hyperoxia.

**Aim:** In a randomized controlled trial, we evaluated oxygenation during general anesthesia with a low (23%) vs a high (80% during induction and recovery, and 40% during maintenance) fraction of inspired oxygen, in newborn infants undergoing surgery.

**Method:** Thirty-five newborn infants with postconceptional age of 35–44 weeks were included (17 infants in low and 18 in high oxygen group). Oxygenation was monitored by transcutaneous partial pressure of oxygen, pulse oximetry, and cerebral oxygenation. Predefined SpO2 safety targets dictated when to increase inspired oxygen.

**Results:** At start of anesthesia, oxygenation was similar in both groups. Throughout anesthesia, the high oxygen group displayed significant hyperoxia with higher (difference−20.3 kPa, 95% confidence interval (CI)−28.4 to 12.2, \( p < .001 \)) transcutaneous partial pressure of oxygen values than the low oxygen group. While SpO2 in the low oxygen group was lower (difference−5.8%, 95% CI −9.3 to −2.4, \( p < .001 \)) during anesthesia, none of the infants spent enough time below SpO2 safety targets to mandate supplemental oxygen, and cerebral oxygenation was within the normal range and not statistically different between the groups. Analysis of the oxidative stress biomarker urinary F2-Isoprostane revealed no differences between the low and high oxygen group.

**Conclusion:** We conclude that in healthy newborn infants, use of low oxygen during general anesthesia was feasible, while the prevailing practice of using high levels of inspired oxygen resulted in significant hyperoxia. The trade-off between careful dosing of oxygen and risks of hypo- and hyperoxia in neonatal anesthesia should be further examined.

**KEYWORDS**

F2-Isoprostanes, hyperoxia, neonatal anesthesia, oxidative stress, oxygenation
1 | INTRODUCTION

The routine of using a high fraction of inspired oxygen (FI\textsubscript{2}O\textsubscript{2}) for preoxygenation during induction of anesthesia aimed to reduce the risk of hypoxemia in newborn infants as well as in older patients. Also, during maintenance of anesthesia, it is common practice to administer a higher FI\textsubscript{2}O\textsubscript{2} than the infant would otherwise need.\textsuperscript{1} Studies in adults have demonstrated that the time to desaturation (<90\%) while handling the airway is increased twofold with an FI\textsubscript{2}O\textsubscript{2} of 100\% compared with 60\%.\textsuperscript{2} Further, in children the time to an eventual decrease in oxygen saturation has been demonstrated to depend on the duration of preoxygenation.\textsuperscript{3} No parallel data exists for the neonatal population but it is reasonable to assume a similar relationship in the neonate. Further, in relation to body weight, newborn infants have a relatively smaller functional residual lung capacity and a higher metabolic rate, two physiological characteristics that will further limit the “oxygen reserve” in an event of apnea or disrupted ventilation. However, there are potential disadvantages with this approach since ventilation with pure oxygen has been shown to induce hyperoxia\textsuperscript{4} which contributes to the formation of lung atelectasis\textsuperscript{5} and reactive oxygen species (ROS) overproduction.\textsuperscript{6} There are also concerns such an overproduction of ROS may induce in vivo oxidative stress. F\textsubscript{2}-isoprostanes are unique compounds formed by nonenzymatic oxidation of arachidonic acid (AA) and are considered to be most reliable biomarkers for assessing oxidative stress in vivo.\textsuperscript{7,8}

In the otherwise healthy newborn, the oxygen delivery is generous and well beyond the demand, and association between oxygen exposure, even brief, is established to have adverse impact.\textsuperscript{9} Outside the operating room (OR), the harm of excess oxygen and hyperoxia to newborn infants is well-established knowledge,\textsuperscript{10} and experimental data indicates that even brief episodes may have negative effects related to oxidative stress due to the eventual formation of oxygen-free radicals.\textsuperscript{11} Altogether, this knowledge has changed clinical practice in the way oxygen is delivered in neonatal care. At present, it is recommended that room air is used for neonatal resuscitation and the most recent guidelines recommend oxygen saturation targets of 90\%–95\% for preterm infants.\textsuperscript{12}

In view of the lack of data on the optimal initial FI\textsubscript{2}O\textsubscript{2} for induction of neonatal anesthesia and the current recommendations for neonatal resuscitation, we hypothesized that anesthesia with low oxygen could be safely implemented and might result in less hyperoxia and risk of oxidative stress than the current standard of care. The present randomized controlled study aimed to investigate the management of anesthesia with low oxygen (LOWOX; 23\%) vs high oxygen (HIOX; 80\% during induction and recovery, 40\% during maintenance) in healthy newborn infants undergoing planned surgery, and further to examine if any of the anesthesia combinations were associated with changes in a marker of oxidative stress.
the LOWOX intervention group and 18 to the HIOX control group using the sealed envelope method. Enrollment was consecutive but limited by the availability of the primary investigator (V.K.) and the study’s assigned anesthesiologist (B.S).

2.2 | Anesthesia procedure and timing

2.2.1 | Induction phase

*Induction* was defined as the time from administration of anesthetic drugs until the completion of intubation. Prior to induction all infants were breathing spontaneously in LOWOX while monitoring was applied. Monitoring of oxygenation (see details below) included two pulse oximeters, a transcutaneous monitor for $pO_2$ and a near-infrared spectroscopy (NIRS) sensor. At induction (0 min), Atropin (0.02 mg/kg) was administered intravenously (i.v.) followed by inhalational anesthesia (Sevoflurane) and neuromuscular blockade (Atracurium 0.5 mg/kg i.v.) in rapid sequence. Infants were ventilated using pressure control mode for 3 min via the anesthesia delivery ventilator (FLOW-I, Maquet, Sweden) with either LOWOX ($FiO_2$ 23%), or HIOX (Figure 1). A positive end-expiratory pressure (PEEP) of 5 cm H$_2$O was used, the peak inspiratory pressures were adjusted to achieve adequate chest movement, and then the infant was orally intubated at 3 min. The $FiO_2$ of 23% in the LOWOX group was mandated by a built-in default setting of the anesthesia ventilator to avoid a too-low end-tidal $O_2$. The time for the intubation procedure was on all occasions 30 s or less.

### TABLE 1 Infant characteristics

|                          | LOWOX ($n = 17$) | HIOX ($n = 18$) |
|--------------------------|------------------|-----------------|
| At birth                 |                  |                 |
| Gestational age (weeks)  | 39 (35–42)       | 39 (36–42)      |
| Birth weight (g)         | 3370 (2160–3655) | 3000 (2290–4300)|
| At day of study          |                  |                 |
| Postconceptional age     | 40 (35–44)       | 40 (36–44)      |
| Postnatal age (days)     | 2 (0–42)         | 2 (0–44)        |
| Weight (g)               | 3300 (2160–5125) | 3160 (2300–5100) |
| Primary diagnosis        | n                | n               |
| Anal atresia             | 2                | 5               |
| Duodenal atresia         | 5                | 2               |
| Esophageal atresia       | 0                | 1               |
| Hirschsprung’s disease   | 1                | 0               |
| Inguinal hernia          | 1                | 1               |
| Intestinal malrotation   | 2                | 1               |
| Omphalocele              | 4                | 3               |
| Pyloric stenosis         | 2                | 3               |
| Urethral valve           | 0                | 2               |

Notes: Values are median (range). LOWOX, 23% $O_2$; HIOX, 80% $O_2$. There are no statistically significant differences between the two groups.

2.2.2 | Maintenance phase

*Maintenance* included the time from completed intubation until the sign-out (initiated by the surgeon at completion of surgery) according to WHO’s checklist for safe surgery had been performed. During maintenance, infants continued receiving Sevoflurane, combined with local anesthetics when appropriate. All surgeries were performed opioid-free, and perioperative analgesia provided with local anesthetics and Sevoflurane. Ventilation was set to pressure-regulated volume control mode for infants >3 kg, and pressure control mode for infants <3 kg with a PEEP of 5 cm and an initial tidal volume of 7 ml/kg, keeping the LOWOX group at $FiO_2$ 23% while the HIOX group received a $FiO_2$ of 40% according to current institutional guidelines.

2.2.3 | Recovery phase

*Recovery* included the time from maintenance to established spontaneous respiration and extubation. After completion of surgery and sign-out, the neuromuscular block was reversed with atropin (0.02 mg/kg) and neostigmin (0.04 mg/kg). Inhalational anesthesia was turned off and the fresh gas flow increased to 5 L/min. The

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**FIGURE 1** Study process and assigned fraction of inspired oxygen ($FiO_2$) for each group. LOWOX, Low oxygen group, HIOX; High oxygen group.
LOWOX group was maintained at 23%, while the FiO\textsubscript{2} in the HIOX group was again adjusted to 80%. Once the infants were regularly triggering breaths, they were extubated. The postoperative course was uneventful in all infants, and none required further respiratory support or supplemental oxygen.

2.3 | Transcutaneous \text{O}_2

The transcutaneous partial pressure of oxygen (TC\text{pO}_2; kPa) was continuously measured using the E5280 probe (TCM 4/40, Radiometer, Denmark) with a probe temperature of 43°C according to manufacturer recommendations and calibrated prior to each patient. The probe was placed on the upper chest and allowed to stabilize for 15 min before recording TC\text{pO}_2.

2.4 | Pulse oximetry (Sp\text{O}_2)

Pulse oximeter (Masimo SET, Masimo Corporation) probes (using an averaging time of 10 s) were placed on the right hand, and on one foot. The reading with a reliable signal was recorded, or if both signals were adequate, the highest was recorded.

2.5 | Near-infrared spectroscopy

A near-infrared spectroscopy (NIRS) oximeter (INVOS 5100C, Covidien) with neonatal sensors was used for measurements of regional cerebral oxygen saturation (rSc\text{O}_2), with the sensor placed on the infant’s forehead, lateral to the midline.

2.6 | F\textsubscript{2}-isoprostanes (8-iso-PGF\textsubscript{2α})—biochemical markers of oxidative stress

Urinary isoprostanes were used as biomarker for oxidative stress.\textsuperscript{7,8} Spot urine samples without any addition of preservatives were collected at three time points, (1) prior to anesthesia (day before or same day), (2) after anesthesia (same day), (3) first postoperative day, and urine samples were stored at −80°C until analysis. The concentration of urinary 8-iso-PGF\textsubscript{2α} (F\textsubscript{2}-isoprostanes) was determined using a validated radioimmunoassay, and the specificity of the assays has previously been established.\textsuperscript{7,8} As the variation in urine flow rate could affect the assessment of urinary 8-iso-PGF\textsubscript{2α} levels, urinary creatinine adjustments with 8-iso-PGF\textsubscript{2α} levels were performed. The urinary concentration of 8-iso-PGF\textsubscript{2α} is expressed as nmol/mmol creatinine.

2.7 | Safety strategy

According to the study protocol, prespecified oxygen saturation targets dictated when/if supplemental oxygen had to be administered. With an oxygen saturation target of Sp\text{O}_2 > 90%, any deviation below this value mandated FiO\textsubscript{2} to be adjusted as follows:

a. Sp\text{O}_2 less than 90% > 5 min: FiO\textsubscript{2} increased in steps of 5% per minute until target reached.
b. Sp\text{O}_2 less than 85% > 2 min or less than 80% for > 1 min: FiO\textsubscript{2} stepwise increased (40–60–80%) until Sp\text{O}_2 > 85%.

2.8 | Data collection and statistical analysis

All procedures were guided by a timer and documented with a camcorder to allow real-time guidance of every step of the procedure and ensure its safety as well as detailed subsequent timing and recording of monitoring data. The data were then collected by the primary investigator (V.K.) from the recorded film and documented in a study protocol at 30-second intervals.

Data were analyzed for three time points during induction: (1) at start of induction (0 min); (2) immediately prior to intubation (3 min); (3) after intubation with infant on ventilator (4 min). Data for the recovery were analyzed at three time points: (1) at initiation of recovery; (2) 3 min before extubation; (3) after extubation. The time from initiation of recovery until extubation was completed was also recorded.

The Mann–Whitney U test was used for analysis of differences in oxygenation and urinary F\textsubscript{2}-isoprostanes levels between the groups while the Student’s t-test was used for comparison of infant characteristics, changes in oxygenation and urinary F\textsubscript{2}-isoprostanes within the groups, and Fisher’s exact test was used for the incidence of hyperoxia. A p-value of less than .05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corp).

3 | RESULTS

3.1 | Pattern of oxygenation

3.1.1 | Induction phase

As expected TC\text{pO}_2 did not differ between the groups at baseline, but at all time points during anesthesia induction, the HIOX group demonstrated a more than twofold higher (difference—10.3 kPa, 95% CI −15.5 to −4.9, p < .001) TC\text{pO}_2 compared with the LOWOX group (Table 2). In parallel, while no infants in LOWOX group demonstrated hyperoxia, it was almost universal in HIOX (Table 2).

The trajectory of the Sp\text{O}_2 values were similar in the two groups from baseline to intubation at 3 min. However, at 4 min, 60s after start of intubation, Sp\text{O}_2 was lower (difference—5.8%, 95% CI −9.3 to −2.4, p < .001) in the LOWOX group than in the HIOX group (Table 2).

Cerebral oxygenation (rSc\text{O}_2) was at all times within the normal range and not statistically different between the groups. There was...
a slight decrease in rScO\textsubscript{2} in both groups during induction (LOWOX: difference—11%, 95% CI 6.6–16, \(p\) < .001, HIOX: difference 14%, 95% CI 7.9–20.1, \(p\) < .001).

### 3.1.2 | Recovery phase

At the end of maintenance/initiation of recovery TCpO\textsubscript{2} was significantly higher (difference—15.2 kPa, 95% CI −23.5 to −6.9, \(p\) < .001) in the HIOX group than in LOWOX group. This difference continued to increase throughout the recovery phase when the HIOX group displayed overt hyperoxia (Table 3). In parallel with the trajectory of SpO\textsubscript{2} during the induction phase, pulse oximetry values were consistently lower in the LOWOX group (all \(p\) < .05) while there was no difference in rScO\textsubscript{2} between the two groups (Table 3). The recovery time was similar in the two groups, being 14 ± 7 and 15 ± 7 min in LOWOX and HIOX, respectively.

### 3.2 | Time and values outside the target SpO\textsubscript{2} range

None of the infants spent enough time below the prespecified safety oxygen saturation targets to mandate supplemental (or increased) FiO\textsubscript{2}.

In the LOWOX group, 6/17 infants demonstrated mild desaturation on one or more occasions during induction, while none of the 18 infants in the HIOX group had a SpO\textsubscript{2} below 90% (Table 4). The episodes of low SpO\textsubscript{2} were in all but one patient very brief. That particular patient, who also had the longest duration of intubation (30s), spent in total 87s with an SpO2 below 90%, including 15s below 80% with a lowest recorded value of 77%.

During recovery, two infants (both in the LOWOX group) had an episode of saturation below 90% (Table 4). One of them (the infant with the lowest gestational age in the investigation) was apneic 30 s after extubation and was ventilated for 1 min before return of regular breathing and a SpO\textsubscript{2} > 90%.

All infants were successfully extubated in the OR as planned and transferred to the NICU for postoperative care without any subsequent need for supplemental oxygen or respiratory support.

### 3.3 | \(F_2\)-isoprostanes (8-iso-PGF\textsubscript{2\alpha})-oxidative stress biomarker

No statistical difference of urinary \(F_2\)-isoprostanes was found between the RA and HIOX groups, nor within the HIOX group. Values of the analyzed urinary \(F_2\)-isoprostanes before anesthesia was in the LOWOX and HIOX group, respectively, 0.88 ± 0.68 and 1.1 ± 1.0 nmol/mmol creatinine, and first postoperative day 1.1 ± 1.4 and 1.0 ± 1.8 nmol/mmol creatinine.

### 4 | DISCUSSION

This randomized controlled trial has for the first time investigated neonatal anesthesia with low oxygen vs standard practice using a high FiO\textsubscript{2}. The data demonstrates that, at least in our hands, anesthesia of otherwise healthy neonates can be managed without the
use of supplemental oxygen. It is also evident that current standard practice using high levels of oxygen for preoxygenation rapidly and uniformly results in significant hyperoxia. Further, this study could not show any significant difference in vivo levels of oxidative stress as measured by urinary F2-isoprostanes levels between LOWOX and HIOX groups, and in HIOX group before and after anesthesia.

The optimal oxygen saturation and safety target limits for neonatal anesthesia are not known. Attempts to define acceptable variations in SpO2, regional cerebral saturation, and their relation, have been made and in relation to this previous work, our data allow interesting comparisons to be drawn. Our regional cerebral oxygen measurements consistently followed the same pattern in both groups. From baseline, cerebral saturation decreased by a mean of 15% during the few minutes of anesthesia induction. This corresponds to what has been previously suggested to represent a mild reduction (11%–20% below baseline). It is noteworthy that this decrease was independent of FiO2 and most likely reflects a pharmacological effect of the inducing agents on cardiac output and/or blood pressure. It has also been demonstrated that mild cerebral desaturation occurs frequently during anesthesia in infants and that also more severe desaturation, as detected by pulse oximetry (SpO2 <70% for more than 3 min), is associated with only mild cerebral desaturation. In this context, our observed changes in oxygenation seems mild at most, with an extent comparable to when preoxygenation is used uniformly.

The potential negative neurologic outcome after pediatric and neonatal anesthesia is a concern. While strong animal experimental

| TABLE 3 | Oxygenation at different time points during recovery |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **LOWOX (n = 17)** | **HIOX (n = 18)** | **Difference [CI 95%]** | **p** |
| TCpO2 (kPa) | | | |
| Initiation of recovery | 8.0 ± 1.7 | 11.5 ± 4.9 | -15.2 [-23.5 to -6.9] | <.001 |
| 3 min before extubation | 8.1 ± 2.8 | 23.1 ± 15.1 | -20.3 [-28.4 to -12.2] | <.001 |
| After extubation | 8.8 ± 2.2 | 28.8 ± 12.1 | -20.0 [-26.3 to -13.8] | <.001 |
| SpO2 (%) | | | | |
| Initiation of recovery | 96 ± 2.5 | 98 ± 1.2 | -2.6 [-3.9 to -1.7] | .001 |
| 3 min before extubation | 96 ± 2.2 | 99 ± 1.4 | -3.1 [-4.8 to -1.3] | <.000 |
| After extubation | 96 ± 2.5 | 99 ± 1.1 | -3.5 [-4.8 to -2.1] | <.000 |
| rScO2 (%) | | | | |
| Initiation of recovery | 77 ± 15 | 80 ± 9.5 | -7.1 [-16.1 to 1.9] | .13 |
| 3 min before extubation | 79 ± 14 | 86 ± 8.5 | -3.6 [-11.5 to 4.3] | .48 |
| After extubation | 82 ± 10 | 87 ± 9.0 | -4.0 [-11.1 to 3.2] | .47 |

Note: Values are mean ± SD.
Abbreviations: CI, confidence interval; LOWOX, 23% O2; HIOX, 80% O2; rScO2, regional cerebral oxygen saturation; TCpO2, transcutaneous partial pressure of O2.

| TABLE 4 | Number of infants with an SpO2 below the prespecified safety targets—episodes and their duration |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Infants (n) | <90% | HIOX | <85% | HIOX | <80% | HIOX |
| Induction | | | | | | |
| Infants (n) | 6 | 0 | 5 | 0 | 3* | 0 |
| Episodes (n) | 11 | 8 | 7 (3–23) | 3 |
| Duration/episode (s) | 8 (2–37) | 7 (3–23) | 10 (5–18) |
| Total time all infants (s) | 87 | 55 | 29 |
| Recovery | | | | | | |
| Infants (n) | 2 | 0 | 1 | 0 | 0 | 0 |
| Episodes (n) | 3 | 1 | 1 | 1 |
| Duration/episode (s) | 11 (4–22) | 11 |
| Total time all infants (s) | 32 | 11 | 11 |

Note: Values are n, or mean (range).
Abbreviations: HIOX, 80% O2; RA, room air.
*Lowest SpO2 recorded 77%.
findings support the notion that anesthesia is harmful to the developing brain; it is not known how this translates to the human infant. Although general anesthesia has been demonstrated to greatly enhance cerebral oxygenation and induce hyperoxia in the newborn, the preoxygenation that was initially described as an optional safety routine has become a universal standard of care. Notwithstanding that supplemental oxygen has an important role in anesthesia and intensive care, its excessive use has been shown to increase mortality in neonates as well as in adults. Maintaining as near-normal physiology as possible during neonatal anesthesia is most likely beneficial and both hypoxia and a too-liberal use of oxygen are best avoided. In parallel with how newborn infants are managed in the NICU, it might be appropriate to use oxygen saturation targets in the OR that have been evaluated for neonatal care. One possible approach could be to restrict the use of a high FiO2 for preoxygenation to those infants with an increased risk of desaturation (pulmonary disease, difficult airway, etc.) rather than exposing all infants in the OR to high levels of oxygen.

F2-isoprostanes, which are chemically stable prostaglandin derivatives, are formed by free-radical-catalyzed nonenzymatic peroxidation of arachidonic acid and are considered to reflect oxidative stress in the setting of high oxygen tension. 8-iso-PGF2α, a major F2-isoprostane, is currently regarded as one of the most reliable indicators of in vivo lipid peroxidation and in vivo oxidative stress. In parallel with previous studies of neonates undergoing surgery, we found no significant difference in urinary F2-isoprostanes levels. However, this does not preclude an involvement of oxidative stress in these patient groups since both anesthesia and oxygen supplementation could potentially affect free-radical formation. It is indeed conceivable that the small sample size and heterogeneity of the included infants in our investigation might have resulted in changes in oxidative status that remained undetected.

The generalizability of our investigation is limited by the rigorous study setting. Ventilation was at all times controlled with use of a PEEP, and the procedure performed by experienced staff including the same pediatric anesthesiologist for all patients; this setting might thus not be applicable to all situations and/or institutions. It should also be pointed out that while we considered all anesthesia procedures to be uneventful, and had a relatively short time required for intubation, it is evident that the oxygen reserve in some infants is small enough to result in desaturation, although brief, in less than a minute.

To summarize, we conclude that general anesthesia in newborn infants can be performed without the use of high levels of supplemental oxygen. The potential benefits of avoiding hyperoxia as well as the risk of hypoxia should be further investigated.

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**Conflict of Interest**

There are no conflicts of interest.

**Ethical Statement**

This study was approved by: Etlprövningsnämnden, Uppsala, Sweden (Approval number 2014/183). Written parental consent was obtained before study inclusion.

**Data Availability Statement**

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author, VK, upon reasonable request.

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**APPENDIX 1**

**Pilot study**

Randomized controlled trial of low vs high oxygen during neonatal anesthesia: Oxygenation, feasibility, and oxidative stress.

**Aim**

To test measurement and data recording procedure and obtain data for calculation of sample size.

**Methods**

*Main outcome measure:* Transcutaneous partial pressure of oxygen (TCpO\(_2\)).

*Subjects:* Six infants with a gestational age of 36\(^{2/7}\)–41\(^{3/7}\) weeks, a birthweight of 3000–3800 g, and a postnatal age of 0–3 days.

*Exposure:* Anesthesia induction with either room air (LOWOX; 23%; \(n = 3\)), or high oxygen (HIOX; 80%; \(n = 3\)). TCpO\(_2\) was recorded after induction of anesthesia.

**Results**

TCpO\(_2\) was 17.1 ± 8.2 and 9.1 ± 2.9 (SD) kPa in LOWOX and HIOX groups, respectively.

**Conclusion**

The estimated effect size is moderate to large. To detect a difference in pO\(_2\) between the groups with a 1:1 allocation, a power of 80%, and a significance level of .05 would require a sample size of at least \(n = 32\).