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RESEARCH REPORT

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 SpO_2 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 F_2-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 (FiO_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 FiO_2 than the infant would otherwise need.[1] Studies in adults have demonstrated that the time to desaturation (<90%) while handling the airway is increased twofold with an FiO_2 of 100% compared with 60%.[2] Further, in children the time to an eventual decrease in oxygen saturation has been demonstrated to depend on the duration of preoxygenation.[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[4] which contributes to the formation of lung atelectasis[5] and reactive oxygen species (ROS) overproduction.[6] There are also concerns such an overproduction of ROS may induce in vivo oxidative stress. F_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*.[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.[9] Outside the operating room (OR), the harm of excess oxygen and hyperoxia to newborn infants is well-established knowledge,[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.[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.[12]

In view of the lack of data on the optimal initial FiO_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.

What is already known about the topic?

The use of high fraction of inspired oxygen induces hyperoxia which might contribute to formation of lung atelectasis, and overproduction of reactive oxygen species.

What new information this study adds?

The use of low oxygen during neonatal anesthesia was feasible, did not result in hypoxia, and avoided the hyperoxia that was invariably demonstrated in infants exposed to a high fraction of inspired oxygen.

2 | MATERIALS AND METHODS

This study was approved by the regional ethical review board (IRB # 2014/183), and in all cases, written parental consent was obtained before study inclusion. The trial was registered prior to patient enrollment at clinicaltrials.gov (ANOXneo study id; NCT02698020, Principal investigator: J.Å., Date of registration: 03/01/2016). This manuscript adheres to the applicable CONSORT guidelines. The study was a prospective randomized trial conducted from March 2016 to May 2018 at the University Children's Hospital of Uppsala, Sweden. The primary outcomes of the trial were the partial pressure of oxygen and the occurrence of hyperoxia ($pO_2 > 13.3$ kPa), and secondary outcome the level of a biomarker of oxidative stress in infants managed with LOWOX vs HIOX throughout the anesthesia.

2.1 | Subjects

Newborn infants with a postconceptional age of less than 44 weeks, admitted to the neonatal intensive care unit (NICU) and scheduled for surgery, and without any prior need of assisted ventilation or supplemental oxygen, were eligible. A total of 35 infants were enrolled in the study, 17 infants to the LOWOX intervention group and 18 to the HIOX control group (Table 1). The groups were similar in background characteristics. The study design necessitated the surgery to be of such character that extubation in the OR prior to returning to the NICU could be expected (Table 1). No previously published data from a comparable population were available on which a calculation of statistical power could be based. Thus, a small pilot study (Appendix 1) was performed that rendered a moderate to large effect size for the primary outcome pO_2. Aiming to detect a difference in the partial pressure of oxygen (pO_2) between the groups with a power of 80% and a significance level of .05 the subsequent calculation yielded a sample size of 16 infants in each group. To allow for a slightly skewed random allocation to the two groups, we a priori chose to include 20 subjects in each study group. A total of 40 infants were eligible and approached for consent. Five families declined participation, leaving 35 included infants (Table 1). Seventeen infants were randomized to

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_2O 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 (weeks)	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 23% FiO_2 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

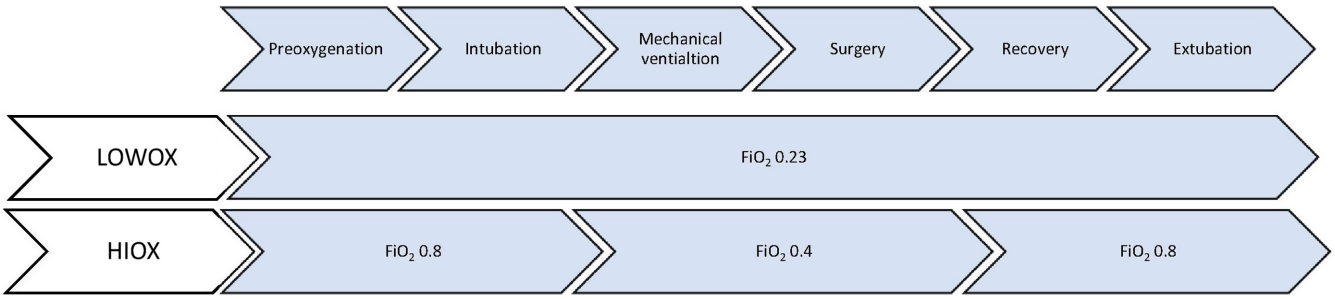

FIGURE 1 Study process and assigned fraction of inspired oxygen (FiO_2) for each group. LOWOX, Low oxygen group, HIOX; High oxygen group.

LOWOX group was maintained at 23%, while the FiO_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 O_2

The transcutaneous partial pressure of oxygen (TCpO2; 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 pO2.

2.4 | Pulse oximetry (SpO_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 ($rScO_2$), with the sensor placed on the infant's forehead, lateral to the midline.

2.6 | F2-isoprostanes (8-iso-PGF2α)—biochemical markers of oxidative stress

Urinary isoprostanes were used as biomarker for oxidative stress.[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-$PGF_{2\alpha}$ (F_2-isoprostanes) was determined using a validated radioimmunoassay, and the specificity of the assays has previously been established.[7,8] As the variation in urine flow rate could affect the assessment of urinary 8-iso-$PGF_{2\alpha}$ levels, urinary creatinine adjustments with 8-iso-$PGF_{2\alpha}$ levels were performed. The urinary concentration of 8-iso-$PGF_{2\alpha}$ 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 $SpO_2 > 90\%$, any deviation below this value mandated FiO_2 to be adjusted as follows:

a. SpO_2 less than 90% >5 min: FiO_2 increased in steps of 5% per minute until target reached.
b. SpO_2 less than 85% >2 min or less than 80% for >1 min: FiO_2 stepwise increased (40–60-80%) until SpO2 > 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_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_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 $TCpO_2$ 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, $p < .001$) $TCpO_2$ 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 SpO2 values were similar in the two groups from baseline to intubation at 3 min. However, at 4 min, 60 s after start of intubation, SpO_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 ($rScO_2$) was at all times within the normal range and not statistically different between the groups. There was

TABLE 2 Oxygenation during the induction phase of anesthesia

	LOWOX ($n = 17$)	HIOX ($n = 18$)	Difference [CI 95%]	p
$TCpO_2$ (kPa)				
At start of induction 0 min	8.1 ± 2	8.2 ± 2.3	−0.3 [−1.8 to 1.3]	.95
Before intubation 3 min	8.6 ± 2.3	18.7 ± 9.9	−10.3 [−15.5 to −4.9]	<.001
End of intubation 4 min	7.4 ± 2.2	18.3 ± 9.7	−11.0 [−16.3 to −5.7]	<.001
Hyperoxia ($pO_2 > 13.3$ kPa[a])				
At start of induction 0 min	0/17	0/18		1.0
Before intubation 3 min	0/17	12/18		<.0001
End of intubation 4 min	0/17	13/18		<.0001
SpO_2 (%)				
At start of induction 0 min	99 ± 1.0	99 ± 1.7	−0.1 [−1.1 to 0.9]	.40
Before intubation 3 min	99 ± 1.2	99 ± 1.8	−0.6 [−1.7 to 0.5]	.77
End of intubation 4 min	93 ± 6.7	99 ± 1.5	−5.8 [−9.3 to −2.4]	<.001
$rScO_2$ (%)				
At start of induction 0 min	86 ± 9.5	85 ± 6.5	−0.4 [−6.3 to 5.6]	.88
Before intubation 3 min	72 ± 7.3	72 ± 10.5	1.2 [−5.7 to 8.0]	.55
End of intubation 4 min	76 ± 8.5	82 ± 12.2	−5.1 [−13.5 to 3.4]	.13

Note: Values are mean ± SD or *n*.

Abbreviations: CI, confidence interval; HIOX, 80% O_2; LOWOX, 23% O_2; $rScO_2$, regional cerebral oxygen saturation; $TCpO_2$, transcutaneous partial pressure of O_2.

[a]Hyperoxia defined as in reference no 1.

a slight decrease in $rScO_2$ 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 $TCpO_2$ 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_2 during the induction phase, pulse oximetry values were consistently lower in the LOWOX group (all $p < 0.5$) while there was no difference in $rScO_2$ 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_2 range

None of the infants spent enough time below the prespecified safety oxygen saturation targets to mandate supplemental (or increased) FiO_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_2 below 90% (Table 4). The episodes of low SpO_2 were in all but one patient very brief. That particular patient, who also had the longest duration of intubation (30 s), spent in total 87 s with an SpO2 below 90%, including 15 s 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 $SpO_2 > 90\%$.

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-$PGF_{2\alpha}$)-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_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 in vivo levels of oxidative stress as measured by urinary F_2-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 SpO_2, regional cerebral saturation, and their relation, have been made[13] 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[13] to represent a mild reduction (11%–20% below baseline). It is noteworthy that this decrease was independent of FiO_2 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 (SpO_2 <70% for more than 3 min), is associated with only mild cerebral desaturation.[13] In this context, our observed changes in oxygenation seems mild at most, with an extent comparable to when preoxygenation is used uniformly.[14]

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
$TCpO_2$ (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
SpO_2 (%)				
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
$rScO_2$ (%)				
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% O_2, HIOX, 80% O_2; $rScO_2$, regional cerebral oxygen saturation; $TCpO_2$, transcutaneous partial pressure of O_2.

TABLE 4 Number of infants with an SpO_2 below the prespecified safety targets—episodes and their duration

	<90%		<85%		<80%	
	RA	HIOX	RA	HIOX	RA	HIOX
Induction						
Infants (n)	6	0	5	0	3[a]	0
Episodes (n)	11		8		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			
Duration/episode (s)	11 (4–22)		11			
Total time all infants (s)	32		11			

Note: Values are n, or mean (range).

Abbreviations: HIOX, 80% O_2; RA, room air.

[a]Lowest SpO_2 recorded 77%.

findings support the notion that anesthesia is harmful to the developing brain[15] it is not known how this translates to the human infant.[16] Although general anesthesia has been demonstrated to greatly enhance cerebral oxygenation and induce hyperoxia in the newborn,[17] the preoxygenation that was initially described as an optional safety routine has become a universal standard of care.[18] Notwithstanding that supplemental oxygen has an important role in anesthesia and intensive care, its excessive use has been shown to increase mortality in neonates[19] as well as in adults.[20] Maintaining as near-normal physiology as possible during neonatal anesthesia is most likely beneficial,[21] and both hypoxia and a too-liberal use of oxygen are best avoided.[22] 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.[23] One possible approach could be to restrict the use of a high FiO_2 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.

F_2-isoprostanes, which are chemically stable prostaglandin derivatives, are formed by free-radical-catalyzed nonenzymatic peroxidation of arachidonic acid[24] and are considered to reflect oxidative stress in the setting of high oxygen tension. 8-Iso-$PGF_{2\alpha}$, a major F_2-isoprostane, is currently regarded as one of the most reliable indicators of in vivo lipid peroxidation and in vivo oxidative stress.[7,8] In parallel with previous studies of neonates undergoing surgery,[25] we found no significant difference in urinary F_2-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.

FUNDING INFORMATION

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CONFLICT OF INTEREST

There are no conflicts of interest.

ETHICAL STATEMENT

This study was approved by: Etikprövningsnämnden, 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

TCpO2 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 $n = 32$.