Supplementary Online Content


**eFigure.** PRISMA flow diagram

**eTable 1.** Brief description of 49 excluded studies in chronological order of publication and reasons for exclusion

**eTable 2.** Brief description of characteristics and outcomes of the studies included in this review

This supplementary material has been provided by the authors to give readers additional information about their work.
Figure. PRISMA Flow Diagram

2836 Records identified through database searching

6 Additional records identified through other sources

1957 Records after duplicates removed

1957 Records screened

1903 Records excluded

54 Full-text articles assessed for eligibility

49 Full-text articles excluded, with reasons for exclusion of each study included in eTable 1

5 Studies included in qualitative synthesis included in eTable 2

5 Studies included in quantitative synthesis (meta-analysis)

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<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for not including</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Coates, A. L., et al. (1982). &quot;Oxygen therapy and long-term pulmonary outcome of respiratory distress syndrome in newborns.&quot; Am J Dis Child <strong>136</strong>(10): 892-895.</td>
<td>Pulmonary function tests were performed on 14 survivors receiving the low O₂ regimen (low O₂ group) and on nine receiving the high O₂ regimen (high O₂ group) ten years after their initial illness. Different PICO; mechanical ventilation was not used in either group.</td>
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<td>3. Bancalari, E., et al. (1987). &quot;Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity.&quot; Pediatrics <strong>79</strong>(5): 663-669.</td>
<td>This study was performed to determine whether the use of continuous transcutaneous oxygen tension (tcPO₂) monitoring could reduce the incidence of retinopathy of prematurity in preterm infants receiving oxygen therapy. As above #2.</td>
</tr>
<tr>
<td>5. (2000). &quot;Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes.&quot; Pediatrics <strong>105</strong>(2): 295-310.</td>
<td>To determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold retinopathy of prematurity (ROP) to reduce the probability of progression to threshold ROP and the need for peripheral retinal ablation. Different PICO.</td>
</tr>
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<td>7. Vento, M., et al. (2001). &quot;Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates.&quot; Pediatrics <strong>107</strong>(4): 642-647.</td>
<td>Oxidative stress markers in moderately asphyxiated term newborn infants resuscitated with either 100% oxygen or room air have been studied for the first time in this work. Different PICO.</td>
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<td>10. Saugstad, O. D., et al. (2003). &quot;Resuscitation of newborn infants with 21% or 100% oxygen: follow-up at 18 to 24 months.&quot; Pediatrics <strong>112</strong>(2): 296-300.</td>
<td>To follow-up children who had been resuscitated at birth with either 21% or 100% oxygen at 24 months for outcome. Different intervention.</td>
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<tr>
<td>11. Askie, L. M., et al. (2003). &quot;Oxygen-saturation targets and outcomes in extremely preterm infants.&quot; N Engl J Med <strong>349</strong>(10): 959-967.</td>
<td>Target functional oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group); this target was maintained for the duration of supplemental-oxygen therapy. Intervention (saturation range) different.</td>
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Studied a system for automatic oxygen control and hypothesized that this system is more effective than routine manual oxygen control in maintaining target arterial oxygen saturation levels. Different PICO


Narrative Review


Objective was to see if the amount of oxygen used during resuscitation at birth triggers events that lead to the subsequent lung injury and if a reduction in oxygen used leads to a reduction in lung injury. Different PICO.


The aim of the study was to determine if neonates resuscitated with room air compared with 100% oxygen in the delivery room were less likely to have hypoxic ischemic encephalopathy and/or death before discharge. Different intervention


A randomized crossover study was performed to determine the most efficient method of applying the sensor. Different PICO


Objective was to determine the clinical benefits and safety of higher PaCO2 goals for ventilated preterm infants. Different Intervention


Different PICO


Narrative Review


To provide data on ventilation, oxygenation and acid-base state from birth to 48 h in very preterm infants treated with lung recruitment maneuver and nasopharyngeal continuous positive airway pressure in the delivery room. Different intervention.


Study comparing transcutaneous oxygen tension or saturation monitoring to variability of oxygenation


Neonates < 32 weeks, compared room air versus 100% O2 resuscitation. Different population, intervention, comparator.


Study compared achievement of a targeted oxygen saturation of 85% at 10 minutes of life when resuscitation was initiated with low or high fractions of inspired oxygen and levels were adjusted according to preductal pulse oxygen saturation values. Different outcome.


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Study evaluating the accuracy of the pulse oximeter used in the BOOST trial. This paper was included in the discussion but not in the data abstraction of the systematic review.


Study evaluating the optimal oxygen titration strategy in infants born at 32 weeks of gestation or less in the delivery room to maintain O2 saturation between 85% and 92%. Different PICO


Narrative review


Narrative Review


Narrative Review


The aim of this meta-analysis was to re-evaluate the evidence in favor of oxygen or room air as the initial gas mixture for neonatal resuscitation in terms of the following outcomes: death, hypoxic/ischemic encephalopathy, and need for tracheal intubation. Different PICO


Review


This study tested the hypothesis that preterm infants randomized to a low vs high O2 saturation target range have a higher incidence of intermittent hypoxemia. Different Outcome.


Narrative Review


This is a study protocol, the objective of this study was to compare the safety and efficacy of resuscitating preterm infants <32 weeks of age with an initial FiO2 of 30% versus 65%.


Review of randomized and observational studies that compare the incidence of ROP in babies with high or low oxygen saturation targeting assisted by pulse oximetry. Not primary RCT


Objective was to determine whether a limited oxygen strategy versus a high oxygen strategy during delivery room resuscitation decreases oxidative stress in preterm neonates (24 – 32 weeks). Different PICO


Editorial


Objective of his trial was to test the hypothesis that a higher pulse oximetric arterial oxygen saturation (SpO2) target range is associated with reduced cerebral tissue oxygen desaturations from baseline during events of hypoxaemia or bradycardia. Different outcome.
| 40. Hartnett, M. E. and R. H. Lane (2013). | “Effects of oxygen on the development and severity of retinopathy of prematurity.” J AAPOS 17(3): 229-234. | This article reviews major studies on oxygen use in preterm infants and the effects on the development of ROP. |
### eTable 2. Brief description of characteristics and outcomes of the studies included in this review*

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Post Hoc</th>
<th>Comments</th>
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<td>SUPPORT: 2010 February 2005-February 2009. 3546 screened; 1316 enrolled</td>
<td>Composite of severe ROP and death before discharge (28.3, 32.1; RR 0.9 (0.76 to 1.06; p=0.21). The 18 to 22 month outcome have been published separately, revealed borderline significant difference in death before assessment (RR 1.25, 95% CI 1.0-1.55, p=0.046); no difference in other outcomes in the two groups.</td>
<td>Rate of oxygen use at 36 weeks less in low SpO2 (p=0.002). BPD among survivors and composite of BPD or death at 36 weeks was no different. Other endpoints no difference</td>
<td>Death before discharge (19.9% vs. 16.2%; RR 1.27 (1.01 to 1.6; p=0.04; NNH 27) and at 36 weeks Severe ROP among, survivors (8.6% vs. 17.9%, (0.37-0.73; P&lt;0.001, NNT = 11)) Trial was not powered to detect an interaction between the target level of SpO2 saturation and the ventilation intervention, this interaction was evaluated anyway, NS P=0.57. They compare the three point difference in mortality to the 4.9% in historical data</td>
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<td>COT: 2013 December 24 2006 to August 25, 2010. Revised software between February and June 2009. 2885 screened; 1201 enrolled</td>
<td>Death before a corrected age of 18 months or survival with one or more of the following: gross motor disability, cognitive or language delay, severe hearing loss, and bilateral blindness. Stratified by center. 51.6% vs. 49.7% - OR 1.08 (0.85-1.37, p=.52) Rates for all components also no different. Variation in outcomes based on center, p=.24. Mortality 16.6% vs 15.3%, OR 1.11 (0.8-1.54)</td>
<td>ROP, brain injury, PDA, NEC, BPD, duration of use of positive pressure and supplemental O2 (no difference in outcomes except significant difference in use of supplemental oxygen, OR 0.8; (CI -1.5 to -0.1, p=0.03)</td>
<td>The consistency of treatment effects over centers was examined by adding treatment center interaction terms to the logistic model which included Rx and center effects, the change in log likelihood provides a global test of homogeneity of treatment effect over centers.</td>
<td>Higher % of infants in the low SpO2 arm received surfactant (89.4 vs 84.7; p=0.02) Higher % of infants in the high SpO2 arm received supplemental O2 before randomization (43.1 vs. 37.7; p=.05). Subgroup analysis based on software--no difference.</td>
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<td>BOOST II†: 2013. March 1, 2006 to December 24, 2010. Revised software December 2008 and May 2009. NZ had closed. 3041 screened 2448 enrolled</td>
<td>Death or serious disability at 2 years corrected for prematurity. 1261 (51.5%) were treated with the original algorithm and 1187 (48.5%) with the use of revised algorithm. Not published for the entire cohort. New Zealand cohort, no difference at 24</td>
<td>Respiratory outcomes, ROP, PDA, acute abdominal problem, change in weight to 36 weeks. Nine long-term outcomes. Infants in the lower group had a reduced rate of Rx for ROP and increased rate of NEC</td>
<td>Revised algorithm death before hospital discharge (23.1% vs. 15.9%; p=0.002) NNH=14. All data combined 19.2% vs 16.6%; RR 1.16, 0.98-1.37; p=0.09)</td>
<td>Prematurely terminated after mortality at 36 weeks from a combined analysis of BOOST and SUPPORT revealed increased mortality in the low saturation arm. The 2 year outcomes have not been published and are awaited. The NZ arm of the trial published their 2 year...</td>
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months.

|                 | outcome recently and that is included as the 5th paper in this review |

*The first number shown in the table refers to low (85-89%) range and the second number to the higher target range (91-95%).
†BOOST II comprised of three trials (BOOST II UK, Australia and New Zealand trials and results were reported together in reference 15.