

Does Room Air Reduce Mortality Among Term Neonates Requiring Respiratory Support at Birth?



TAKE-HOME MESSAGE

Room air is associated with reduced short-term mortality compared with 100% FiO₂ for neonates greater than 35 weeks' gestation who require respiratory support at birth.

METHODS

DATA SOURCES

Meta-analysis authors identified quasi-randomized controlled trials and nonrandomized trials from Ovid MEDLINE, EMBASE, the Cumulative Index of Nursing and Allied Health, and the Cochrane Central Register of Controlled Trials; searched reference lists of the International Liaison Committee on Resuscitation (ILCOR) 2010, 2015 Consensus on Science With Treatment Recommendations, and other systematic reviews on the topic; evaluated trial registries; and searched the first 200 hits of Google Scholar.¹ Authors limited the literature search to studies from 1980 to December 11, 2017.

STUDY SELECTION

Pairs of independent reviewers independently screened titles and abstracts. They then independently reviewed full-text articles, with final decisions for inclusion made by consensus. Investigators included quasi-randomized controlled trials and observational studies comparing low and high initial oxygen concentration for respiratory support at birth. The authors included studies in which

EBEM Commentators

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This review does not reflect the views or opinions of the US government, Department of Defense or its components, US Army, US Air Force, Brooke Army Medical Center, or San Antonio Uniformed Services Health Education Consortium Emergency Medicine Residency Program.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Welsford M, Nishiyama C, Shortt C, et al. Room air for initiating term newborn resuscitation: a systematic review with meta-analysis. *Pediatrics*. 2019;143:e20181825.**

Results

Outcomes in neonates resuscitated with room air versus 100% FiO₂.

Outcome	No. of Studies (No. of Patients)	Relative Effect, RR (95% CI)	NNT	Evidence Quality (GRADE)	Heterogeneity (I ²), %
Short-term mortality	7 (1,469)	0.73 (0.57–0.94)	22	Low	0
NDI	2 (360)	1.41 (0.77–2.60)	—*	Very low	0
HIE	5 (1,359)	0.90 (0.71–1.14)	—*	Low	8

RR, Relative risk; CI, confidence interval; NNT, number needed to treat; NDI, neurodevelopmental impairment; HIE, hypoxic ischemic encephalopathy.

*NNT calculation not possible for these outcomes.

The meta-analysis included 12 studies comprising 2,164 patients. Six studies were quasi-randomized controlled trials based on alternating days, and 6 were randomized controlled trials, although only 2 were fully randomized with allocation and intervention blinding. Sample sizes ranged from 44

to 609 patients, with mean and median gestational age ranging from 35.3 to 40.5 weeks. Study FiO₂ included room air (21% FiO₂) or 100% FiO₂. None of the included studies used intermediate FiO₂ values. The proportions of subjects undergoing intubation and mechanical ventilation ranged

greater than 75% of patients were at greater than 35 weeks' gestation.

DATA EXTRACTION AND SYNTHESIS

Author pairs independently extracted data from included studies. The primary outcome was short-term all-cause mortality (in-hospital or up to 30 days postnatal). Secondary outcomes included long-term mortality (1 to 3 years), neurodevelopmental impairment, and hypoxic ischemic encephalopathy. Reviewers used a random-effects model for analysis with pooled unadjusted risk ratios and 95% confidence intervals, and they calculated numbers needed to treat when possible. The authors evaluated risk of bias with the Cochrane Risk of Bias Tool for randomized controlled trials and the Risk of Bias in Non-randomized Studies of Interventions tool for observational studies.^{2,3} They evaluated heterogeneity with the I^2 statistic and assessed evidence certainty for each outcome, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Sensitivity analyses were completed when inclusion of one or more studies was uncertain because of high risk of bias, incongruent allocation, significant heterogeneity, or adjusted and nonadjusted analyses. Subgroup analyses were planned according to gestational ages and specific F_{iO_2} ranges.

from 10% to 51%. The authors included 7 studies with 1,469 patients for the meta-analysis of the primary outcome. Results demonstrated a significant reduction in mortality with room air (Table). Survival in the room air group was 90%, compared with 85.4% in the 100% F_{iO_2} group,

correlating to an absolute survival benefit of 4.6% (95% confidence interval 1.0% to 7.3%) and a relative survival benefit of 27%. Heterogeneity was low for this primary outcome. Results were similar in the sensitivity analysis. Most studies demonstrated high risk of bias, and evidence quality was low because of risk of bias, inconsistency, and imprecision.

Commentary

Precipitous delivery in the emergency department (ED) is relatively uncommon, occurring in less than 1% of total births.⁴ However, a precipitous delivery in the ED setting is a stressful event. Almost 10% of newborns require some form of resuscitation at birth, and 1% require significant resuscitation measures, including intubation and compressions.⁵ Emergency provider knowledge of appropriate neonatal resuscitation measures is imperative to optimize care.

Before 2000, resuscitation guidelines recommended 100% F_{iO_2} for newborn respiratory support.⁶ However, hyperoxemia caused by high F_{iO_2} results in the formation of free radicals, which can damage the lungs, brain, eyes, and other organs.⁷ Hypoxemia may also lead to harm. Literature in the early 2000s suggested no harm with room air resuscitation in term neonates, but also potentially an improvement in short-term mortality.⁸ In accordance with this literature, in 2010 and 2015 ILCOR recommended using room air for the initial resuscitation of term neonates.^{9,10}

This meta-analysis is a major component of the ILCOR Consensus on Science With Treatment Recommendations.^{1,9,10} The last ILCOR analysis of room air versus oxygen therapy was completed in 2010, before the use of GRADE methodology for the ILCOR reviews.⁹ This meta-analysis analyzed the present data in accordance with GRADE methodology and demonstrated a benefit for short-term mortality with room air resuscitation.¹ No significant difference was found for room air in regard to hypoxic ischemic encephalopathy or neurodevelopmental impairment. Results are similar to those of previously published meta-analyses.^{8,11}

This meta-analysis has several limitations.¹ Despite the mortality benefit of room air resuscitation in term neonates, there have been no new studies published since 2007. Because current neonatal resuscitation techniques include continuous oxygen saturation monitoring and oxygen titration to achieve desired oxygen saturations, it is unclear whether studies in contemporary settings would yield similar findings. Evidence certainty is low or very low according to GRADE methodology. Out of 10 trials, 8 had high risk of bias, 5 were quasi-randomized controlled trials based on alternating days, and 8 did not possess personnel blinding or allocation concealment. Mortality rates ranged significantly across studies, from 1.5% to 18%, and studies with higher mortality received greater weight in the analysis with greater sample sizes. Readers should use caution in interpreting the neurodevelopmental impairment

and hypoxic ischemic encephalopathy results. The evidence evaluating neurodevelopmental impairment comprised small sample sizes. The pathogenesis of hypoxic ischemic encephalopathy is complex, and postbirth interventions may be unlikely to have a material influence on this outcome.¹² Finally, no studies evaluated intermediate oxygen concentrations between room air and 100% FiO₂, and it is not known whether room air is superior to intermediate FiO₂ levels.

According to these results with low evidence certainty, room air reduces short-term mortality compared with 100% FiO₂ among term neonates requiring respiratory support at birth. Despite the low-quality evidence, these results are consistent across studies with low heterogeneity. The effect of intermediate FiO₂ levels is not known and may benefit from further study.

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