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State of the Art Review: Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants

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Abstract

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory complication of preterm birth. Preterm infants are at risk for acute lung injury immediately after birth, which predisposes to BPD. In this article, we review the current evidence for interventions applied during neonatal transition (delivery room and first postnatal hours of life) to prevent BPD in extremely preterm infants: continuous positive airway pressure (CPAP), sustained lung inflation, supplemental oxygen use during neonatal resuscitation, and surfactant therapy including less-invasive surfactant administration (LISA)

Preterm infants should be stabilized with CPAP in the delivery room, reserving invasive mechanical ventilation for infants who fail non-invasive respiratory support. For infants who require endotracheal intubation and mechanical ventilation soon after birth, surfactant should be given early (<2 hours of life). We recommend prudent titration of supplemental oxygen in the delivery room to achieve targeted oxygen saturations. Promising interventions that may further reduce BPD, such as sustained inflation and non-invasive surfactant administration, are currently under investigation.

Keywords

bronchopulmonary dysplasia; preterm; infant; resuscitation; surfactant; continuous positive airway pressure; sustained inflation; oxygen

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Background

Extremely preterm infants are at high risk for acute lung injury and subsequent chronic lung disease, or bronchopulmonary dysplasia (BPD). BPD affects approximately 25%–40% of surviving very low birth weight (VLBW) infants, (1,2) with the highest incidence among those born at the lowest gestational ages. (3,4) BPD is associated with impaired lung function that persists into adolescence and adulthood. (5–8) In addition, BPD is an important risk factor for adverse non-respiratory outcomes including growth failure, (9,10) neurodevelopment impairment, (11,12) and poor school-age performance. (13)

Considerable data suggest that early lung and systemic inflammation contribute to the pathogenesis of BPD. (14–17) These discoveries led to significant research into early postnatal interventions to prevent or ameliorat early lung inflammation and injury in extremely preterm infants. Immediately after birth, the newborn infant must open and aerate the lung to initiate the transition from a fetal to a post-natal circulation and physiology. However, most extremely preterm infants struggle to independently aerate the lung, owing to a compliant chest wall, (18,19) weak respiratory muscles, altered epithelial sodium channels, (20) and immature surfactant. (21) Consequently, most extremely preterm infants require positive pressure ventilation and/or supplemental oxygen after birth. Although these therapies are often necessary to ensure adequate gas exchange, they may induce acute lung injury from baro- and volutrauma and oxygen free radical formation. Therefore, ideal strategies for BPD prevention should start immediately after preterm birth to limit lung injury and oxidative stress.

About This Article

The focus of this narrative review is an analysis of the current literature describing interventions applied during neonatal transition to prevent BPD in extremely preterm infants. We present the current evidence for therapies used in the delivery room or initial hours of life: continuous positive airway pressure (CPAP), sustained lung inflation, supplemental oxygen use during resuscitation, surfactant therapy (via endotracheal tube), and less-invasive surfactant administration (LISA). Subsequent therapies to prevent BPD have been reviewed elsewhere and are not the focus of this article. (22–24)

We included high-quality randomized controlled trials (RCTs), meta-analyses, and key observational studies. Further, we conducted a meta-analysis of published RCTs comparing LISA versus control therapies in infants born ≤32 weeks gestational age (GA) with a reported outcome of BPD or the composite of BPD or death as an outcome. This analysis was performed with Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

1. CPAP

Use of non-invasive continuous positive airway pressure (CPAP) immediately after birth facilitates lung recruitment and formation of a functional residual capacity (FRC). Non-invasive CPAP mitigates lung injury by avoiding baro-volu-trauma from mechanical ventilation or atelecto-trauma that can result from repeated collapse and expansion of the

alveoli during room air breathing. Early observational data from 1987 suggested that aggressive early use of CPAP reduced BPD. (25) Protocols describing the successful use of CPAP for delivery room resuscitation of extremely low birth weight (ELBW) infants with selective intubation and surfactant administration reserved for infants who failed CPAP followed soon after. (26)

Some 10–15 years after these initial descriptions, several large multicenter randomized trials of respiratory management after birth compared an initial strategy of early CPAP with immediate intubation and surfactant administration. The largest of these were COIN, (27) SUPPORT, (28) and the Vermont Oxford Network delivery room management trial. (29)

In the COIN trial, Morley et al. randomized 610 infants from 25 to 28 $^{6/7}$ weeks gestation to initial respiratory management of either initial CPAP therapy or mechanical ventilation. (27) The SUPPORT trial enrolled 1316 infants between 24–27 $^{6/7}$ weeks gestation who were randomized before birth to initial CPAP therapy with subsequent selective surfactant administration and a limited ventilation strategy versus mechanical ventilation and prophylactic surfactant therapy. (28) Last, in the Vermont Oxford Network trial, Dunn et al. randomized 648 infants between 26–29 $^{6/7}$ weeks gestation to the following modes of respiratory support: prophylactic surfactant followed by mechanical ventilation, prophylactic surfactant followed by extubation to CPAP, or initial CPAP therapy with selective surfactant treatment. (29)

Many study design elements varied between these trials, including enrollment size, the gestational ages of enrolled infants, antenatal versus postnatal randomization, timing of respiratory interventions, and initial CPAP settings (ranging from 5cm H_2O to 8cm H_2O). Despite these differences, all three trial results were consistent for the outcome of BPD. Each trial demonstrated a non-significant reduction in the rate of death or BPD at 36 weeks PMA among infants treated with CPAP, compared to empiric intubation and mechanical ventilation. In pooled analyses of these RCTs, there was a small, but statistically significant reduction in the risk for death or BPD in the CPAP treated infants. The NNT reported by these meta-analyses (some of which included smaller RCTs) ranged from 20–35. (30–32)

While the rate of pneumothorax was higher in CPAP-treated infants in the COIN trial, (27) neither of the other trials reported increased risk for air leaks among infants treated with initial CPAP. In meta-analysis, initial CPAP with selective surfactant was not associated with increased risk for pneumothorax or other adverse events. (31,32)

Based on these findings, the American Academy of Pediatrics Committee on Fetus and Newborn subsequently published a policy statement concluding that, “the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy.” (33)

2. Sustained Inflation

Sustained inflation (SI) is a lung recruitment strategy used immediately after birth. SI holds an inflating pressure for a prolonged duration to achieve lung fluid clearance and to establish

the FRC. In 1981, Vyas et al. described a 5-second SI to asphyxiated term newborns after birth. (34) Subsequent observational studies demonstrated the feasibility and safety of performing SI in preterm infants during neonatal transition.

Five randomized trials of SI in extremely preterm infants have been published to date (Table 1). (35–39) Harling et al. randomized 52 infants <31 weeks gestation to receive either a 5-second SI or a 2-second "conventional" lung inflation as the initial positive pressure inflation delivered after birth. (35) There were no significant differences between groups for the primary outcome, bronchoalveolar lavage cytokine levels, or secondary outcomes of death, BPD, or major neonatal morbidities. (35) Since there was only a 3-second difference in duration of the initial lung inflation, the SI maneuver in this trial may not have been long enough to demonstrate significant differences between groups.

In a RCT stopped early for slow recruitment, Lindner et al. randomized 61 preterm infants to treatment with up to three 15-second SIs vs. intermittent positive pressure ventilation (IPPV) with positive end expiratory pressure (PEEP). (36) There was no significant difference between treatment groups in the primary outcome, intubation in the first 48 hours of life, or secondary outcomes of death or chronic lung disease. (36)

te Pas et al. enrolled 207 infants <33 weeks gestation who required positive pressure ventilation after birth in a single-site RCT comparing one to two SIs (10 seconds each) with IPPV. (37) Infants treated with SI experienced a reduced rate of the primary outcome, intubation in the first 72 hours of life, and the secondary outcome of moderate/severe BPD (9% vs. 19%, OR 0.41, 95% CI 0.18–0.96). Unfortunately, different interfaces and respiratory devices were used between treatment groups, making it difficult to isolate SI as the single cause of improved outcomes. (37)

The multisite SLI (Sustained Lung Inflation) trial randomized infants between 25–$28^{6/7}$ weeks gestation to receive up to two 15-second SIs or nasal CPAP, with subsequent resuscitation according to Neonatal Resuscitation Program guidelines. (38) The primary outcome of this trial, mechanical ventilation within the first 72 hours after birth, was significantly lower in infants treated with SI. This trial was not powered for the outcome of BPD, and BPD rates did not significantly differ between groups. (38)

Jiravisitkul et al. performed a single-site RCT of 81 infants between 25–32 weeks gestation who were randomized to receive up to two 15-second SIs or IPPV with subsequent resuscitation per NRP guidelines. (39) The mean fraction of inspired oxygen 10 minutes after birth- a primary outcome- was lower in the SI group compared with infants in the IPPV group. There were no significant differences in the other primary outcomes (heart rate and SpO_2 in the first 10 minutes of life, or rates of delivery room intubation) between groups. There was no significant difference between treatment groups in the secondary outcome of BPD. (39)

A meta-analysis, comprising 611 preterm infants from four of these trials, found no significant differences in the rates of BPD, death, or the composite outcome of BPD or death among those treated with SI compared to the control therapy. (40) However, these results should be interpreted cautiously, as the individual trials varied considerably with regards to

the duration and peak pressures of the SI, the administered control therapies, resuscitation devices, and demographic characteristics of the enrolled infants (Table 1). Two ongoing trials of SI with the primary outcome of BPD or death will provide important information on the safety and efficacy of SI for the prevention of BPD in extremely preterm infants. (41,42)

3. Supplemental Oxygen during Resuscitation

The transition from the relatively hypoxemic fetal state to a normal post-natal oxygen saturation (SpO_2) is a gradual process after birth. To adequately support gas exchange while avoiding hyperoxia-related toxicity to developing organs, such as the lungs and retina, clinicians try to judiciously regulate supplemental oxygen use in preterm infants. This effort is hampered by the lack of robust data on the normal SpO_2 transition in extremely preterm infants, which in turn complicates efforts to determine the optimal approach to FiO_2 titration after birth.

Dawson et al. published nomograms of SpO_2 after birth, which were generated from 468 infants who did not require respiratory support after birth. (43) However, only 39 (8%) of the infants included in the Dawson curves cohort were born preterm (<32 weeks GA). To address this gap, Vento et al. recorded serial SpO_2 measurements in 102 preterm infants (median GA 29 weeks) who were stabilized using CPAP without supplemental O_2 after birth. Infants in that study achieved reference values of SpO_2 faster than the preterm infants in Dawson's study (who received no respiratory support). (44) In contrast, Mian et al. found that rise in SpO_2 lagged behind both the Dawson and Vento nomograms, in their cohort of 55 preterm infants (mean GA 31 weeks) supported on CPAP, despite provision of supplemental oxygen to many of these infants. (45) Importantly, the normative ranges for SpO_2 rise described in all these studies were derived mostly in moderately preterm infants. They therefore may not be generalizable to the most extremely preterm infants, who are at highest risk for both impaired gas exchange due to immature lungs as well as injury from oxygen toxicity.

Several RCTs have compared an initial approach of low versus high oxygen administration during delivery room resuscitation of preterm infants. (46–54) These trials varied considerably in study design and many of are limited by small sample sizes and use of only very proximal outcomes (Table 2). Two of these RCTs reported a significant reduction in BPD among infants in whom resuscitation was initiated with lower FiO_2. (49,52) However, a meta-analysis comprising RCTs conducted in preterm infants (≤32 weeks GA) demonstrated no significant difference in the risks for BPD (RR 1.11, 95% CI 0.73–1.68) or mortality (RR 0.62, 95% CI 0.37–1.04) between infants treated with low versus high initial concentrations of supplemental oxygen. (55) More recently, Oei et al. performed a meta-analysis restricted to RCTs comparing low (≤ 0.3) vs. high (≥0.6) FiO_2 for resuscitation in infants born ≤28 weeks GA. (56) There was no significant difference between groups for the outcomes of BPD among survivors (37% low oxygen vs. 41% high oxygen, RR 0.88, 95% CI 0.68–1.14) or mortality (14% low oxygen vs. 12% high oxygen, RR 0.99, 95% CI 0.52–1.91). (56)

The Oei meta-analysis included results from the TO_2RPIDO trial, which randomized infants <32 weeks gestation to delivery room resuscitation started with 21% vs. 100% oxygen.

(54)This was an early-stopped trial, which ceased recruitment after just 292 of the targeted 1986 subjects were recruited (of which 287 were included in the analysis). An un-prespecified subgroup analysis of infants <28 weeks gestation in this trial demonstrated higher mortality in the 21% FiO_2 group (22% vs. 6%, p =0.01). (54) In an observational study, Rabi et al. studied 2,326 infants ≤ 27 weeks GA born in Canada before and after local practice changed from initiating resuscitation with 100% FiO_2 to lower oxygen concentrations (typically 21–40%) with subsequent titration. (57) Rates of BPD were similar between the two epochs. However, the composite outcome of death or severe neurologic injury was significantly more frequent among infants resuscitated with an initially lower FiO_2 (adjusted OR 1.36, 95% CI 1.11–1.66). (57)Results from both of these studies should be interpreted cautiously, due to limitations from stopping early (58) (the TO_2RPIDO trial) (54) and the before/after study design relying on an exposure of reported policy changes (Rabi et al.). (57)

While the pooled available data do not suggest that initial FiO_2 during resuscitation influences the outcome of BPD, the optimal initial concentration of supplemental oxygen used during neonatal resuscitation and time to reach “normal” SpO2 in extremely preterm infants remains an important evidence gap. The 2015 International Liaison Committee on Resuscitation recommended starting resuscitation for preterm infants with a low FiO_2 concentration (21–30%), but acknowledged the need for more evidence.(59) The ongoing PreSOX trial (60) may provide more information about the optimal use of oxygen during resuscitation to minimize mortality and morbidity in preterm infants.

4. Surfactant Administration after Standard Endotracheal Intubation

Beginning in the 1980s, several high-quality RCTs assessed the safety and timing of surfactant administration in preterm infants. (61–63) Early RCTs demonstrated that administration of surfactant to preterms with established RDS reduced pulmonary air leak and lowered the risk of death or supplemental oxygen use at 28 days of age (the standard definition of BPD at that time). (61–63) Subsequent studies found that prophylactic administration of surfactant soon after birth also reduced pulmonary morbidity and improved BPD-free survival. (61,62) However, most of these RCTs were conducted prior to the routine use of antenatal corticosteroids and aggressive use of non-invasive CPAP. As discussed above in the section on CPAP, prophylactic intubation and surfactant administration, compared with early non-invasive CPAP therapy, does not reduce BPD risk in preterm infants.(30–32)

Unfortunately, stabilization with non-invasive respiratory support is not possible in all preterm infants. Up to 65% of spontaneously breathing extremely preterm babies require intubation and mechanical ventilation despite early CPAP therapy.(31) In these instances, early rescue surfactant therapy is appropriate. Providing early rescue surfactant (within the first 2 hours of life) to mechanically ventilated preterm infants, as compared to delayed surfactant administration (after second hour of life), reduces the risk of BPD (RR 0.69, 95% CI 0.55–0.86) and the composite of death or BPD (RR 0.83, 95% CI 0.75–0.91). (64)

When surfactant is indicated, there are several animal-derived (modified or purified from bovine or porcine lungs) and synthetic formulations available for use. Animal-derived surfactants compared to first-generation protein free surfactants are associated with a marginal reduction in mortality (RR 0.89, 95% CI 0.79 to 0.99) and death or BPD (RR 0.95, 95% CI 0.91 to 1.00). (65)Meta-analysis of trials comparing modified bovine mined lung surfactant to porcine minced lung surfactant raised concern that bovine surfactant may increase risk for mortality, BPD, and other adverse outcomes. (66) However, in a subgroup analysis, the improvement in morbidity and mortality risk was limited to the trials using a higher initial dose of porcine minced lung surfactant (> 100mg/kg). (66) It is uncertain whether the differences in outcome risks are from differences in the surfactant dose or extraction source. A second-generation synthetic surfactant (lucinactant) containing a peptide analog of surfactant protein-B is also now available and has similar efficacy as animal-derived products. (67,68)

To maximize the potential benefits of early surfactant administration without undergoing prolonged mechanical ventilation, Victorin et al. introduced the technique of INtubation, SURfactant administration during brief mechanical ventilation, followed by Extubation (INSURE approach). (69) Initial RCTs found that the INSURE approach compared to selective administration of surfactant to infants with established RDS reduced the need for mechanical ventilation and use of supplemental oxygen at 28 days of life. (70) However, when compared to early stabilization with CPAP alone, INSURE does not reduce BPD. In a meta-analysis of 9 RCTs that included a total of 1551 preterm infants, Isayama et al. reported that INSURE compared to CPAP did not significantly affect the risk for death or BPD (RR 0.88, 95% CI 0.76–1.02). (71)

5. Less Invasive Surfactant Administration

In an effort to avoid standard endotracheal intubation, several less invasive techniques of surfactant administration have been developed. These include intratracheal instillation of surfactant with a thin catheter (e.g. nasogastric tube), aerosolized administration, intrapartum pharyngeal instillation, and delivery via a laryngeal mask airway (LMA). (72)Of these strategies, surfactant instillation via thin catheter, often referred to as less invasive surfactant administration (LISA) or minimally invasive surfactant therapy (MIST), is the most studied. Verder et al. first published their experience with LISA in the early 1990s. (73) In a large, multi-center observational study (n=2,206) of preterm infants treated with LISA versus matched controls, LISA was associated with lower rates of mechanical ventilation (41% vs. 62%, $p<0.001$) and death or BPD (14% vs. 21%, $p < 0.001$). (74)

Four RCTs conducted in extremely preterm infants compared LISA to surfactant administration via endotracheal tube (3 versus INSURE, 1 versus continued mechanical ventilation after surfactant therapy), (75–78) and one compared LISA to ongoing nasal CPAP therapy. (79) Here, we report a meta-analysis of data combined from these five RCTs (total n=857). Using data combined from all 5 trials, LISA versus control therapy reduced the risk for BPD among survivors to at least 36 weeks PMA (RR 0.70, 95% CI 0.50 to 0.97; typical risk difference −0.05, 95% CI −0.10 to −0.01; number needed to treat [NNT] 19; 95% CI 10 to 189) (Figure 1) and the composite of death or BPD (RR 0.74, 95% CI 0.58 to

0.94; typical risk difference −0.07; 95% CI −0.12 to −0.01; NNT 15; 95% CI 8 to 70) (Figure 2). When compared to INSURE therapy alone (3 trials, n=426), LISA also reduced the risk for death or BPD (RR 0.63, 95% CI 0.42 to 0.93; typical risk difference −0.09, 95% CI −0.16 to −0.015; NNT 12, 95% CI 6 to 66) but not BPD among survivors (RR 0.65, 95% CI 0.35 to 1.19, typical risk difference −0.04; 95% CI −0.10 to 0.02). Of note, one published RCT comparing LISA to INSURE (n=38) was excluded from this analysis owing to enrollment of moderate and extremely preterm infants (GA < 35 weeks). (80)Two meta-analyses inclusive of this RCT were recently reported. (81,82)

Isayama et al. recently reported a Bayesian random-effects network meta-analysis evaluating the efficacy of 6 early ventilation strategies (mechanical ventilation, nasal CPAP, non-invasive positive pressure ventilation, INSURE, LISA, and nebulized surfactant administered via LMA) for prevention of BPD in infants born less than 33 weeks gestation. (83) This approach allowed for simultaneous estimation of the relative effects of multiple interventions regardless of whether they were directly compared in individual trials. The study results indicated that LISA was associated with the largest reduction in the risk for death or BPD (OR 0.49; 95% Credible Interval 0.30–0.79) of any of the evaluated interventions. (83) However, the authors noted the findings were limited by the overall low quality of the available evidence. An ongoing trial (anticipated n=606 for a primary composite outcome of death or physiological BPD) comparing LISA to sham treatment in extremely preterm infants without a history of prior intubation will provide additional important data on this topic. (84)

6. Other strategies

Intratracheal budesonide

Yeh et al. recently randomized 265 VLBW infants with RDS who were mechanically ventilated in the first four hours of life to treatment with intratracheal surfactant versus intratracheal budesonide and surfactant. (85) Infants treated with budesonide and surfactant experienced a significant reduction in the outcome of death or BPD (any supplemental O_2 requirement) at 36 weeks (42% vs. 66%, $p<0.001$). (85) Further, interleukin concentrations in tracheal aspirates were transiently lower among infants in the intervention arm, suggesting intratracheal budesonide may diminish BPD risk through local anti-inflammatory effects. (85)Notably, the effect size of this trial is rather large (number needed to treat, 4.1; 95% CI 2.8–7.8). (85) Thus, while these study results are promising, further large RCTs of intratracheal budesonide plus surfactant are needed before this therapy should be introduced into clinical practice.

Caffeine

In the Caffeine for Apnea of Prematurity (CAP) trial, over 2000 infants with birth weight 500 to 1250 grams were randomized to receive to caffeine or placebo within the first 10 days of life. (86) Infants randomized to caffeine experienced significantly less BPD than placebo infants, which was largely attributed to the fact that caffeine-treated infants received an average of 1 less week of positive pressure ventilation.

Caffeine is now a standard of care therapy in the respiratory management for preterm infants. Early initiation of caffeine is especially critical in the CPAP era, as more preterm infants are managed via non-invasive support immediately after birth and require a sustained respiratory drive to avoid intubation and mechanical ventilation. (87) A meta-analysis comprising both cohort studies and RCT demonstrated that early caffeine administration is association with a reduction in BPD, when compared with later administration. The timing of "early" caffeine administration varied from the first 2 hours after birth to the first three days after birth. (88)

Two small RCTs demonstrated that caffeine administration within the first minutes (89) to first 2 hours of life (90) is feasible and may improve short-term physiologic outcomes. (89,90) Neither trial was designed or powered to detect differences in BPD. While caffeine therapy should be administered early in the NICU to prevent BPD in preterm infants, there are insufficient RCT data to recommend immediate caffeine administration in the delivery room to prevent BPD.

Conclusions

Acute lung injury sustained in the immediate perinatal period directly contributes to the development of BPD in premature infants. Strategies to decrease lung injury and inflammation should begin prior to and continue following preterm delivery (Box). Initial stabilization of all infants at risk for RDS should begin with CPAP, reserving endotracheal intubation and surfactant administration for infants who fail non-invasive support. Prudent titration of supplemental oxygen in the delivery room is also recommended. Promising interventions that may further reduce BPD risk are currently under investigation and include sustained inflation and non-invasive surfactant administration.

Box

Summary of Evidence for Perinatal Interventions to Prevent BPD

Continuous Positive Airway Pressure (CPAP) vs. Mechanical Ventilation

- Evidence: Cochrane meta-analysis of 3 large RCTs (n=2,358) reporting outcome of BPD or death at 36 weeks PMA (32)
- Results: Primary CPAP therapy compared with mechanical ventilation reduced the risk of BPD/death.
- Treatment Effect: Relative Risk 0.89 (95% CI: 0.81–0.97)
- Number Needed to Treat: 20 (95% CI: 11–100)

Sustained Inflation vs. Intermittent Positive Pressure Ventilation or CPAP

- Evidence: Meta-analysis of 4 RCTs (n= 611 infants) comparing SI with IPPV or CPAP reporting the outcome of BPD or death at 36 weeks PMA (40)
- Results: Neither SI or IPPV was superior to reduce the risk of BPD/death.
- Treatment Effect: Relative Risk 0.92 (95% CI: 0.66–1.29)

Supplemental Oxygen during Delivery Room Resuscitation

- Evidence: Meta-analysis of 10 RCTs (n=677 infants ≤32 weeks gestation) comparing low (≤30%) with high (≥60%) initial FiO_2 for delivery room resuscitation reporting outcome of BPD (55)
- Results: Neither approach to supplemental FiO_2 was superior to reduce the risk of BPD
- Treatment Effect: Relative Risk 1.11 (95% CI: 0.73–1.68)

Surfactant

INSURE vs. nasal CPAP

- Evidence: Meta-analysis of 6 RCTs (n=1,250) reporting the outcome of BPD or death at 36 weeks PMA (71)
- Results: Neither INSURE or nasal CPAP was superior to reduce the risk of BPD/death.
- Treatment Effect: Relative Risk 0.88 (95% CI: 0.76–1.02)

Early (< 2hr of life) vs. Late (≥ 2hr of life) administration among infants receiving invasive mechanical ventilation

- Evidence: Cochrane meta-analysis of 3 RCTs (n=3,050) reporting the outcome of BPD or death at 36 weeks PMA (64)
- Results: Early compared with late surfactant reduced the risk of BPD/death.
- Treatment Effect: Relative Risk 0.83 (95% CI: 0.75–0.91)
- Number Needed to Treat: 16 (95% CI: 11–34)

Less Invasive Surfactant Administration (LISA) vs. all control therapies

- Evidence: Meta-analysis of 5 RCTs (n=857) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)
- Results: LISA compared with control therapy reduced the risk of BPD/death.
- Treatment Effect: Relative Risk 0.74 (95% CI 0.58–0.94).
- Number Needed to Treat: 15 (95% CI 8–70)

Less Invasive Surfactant Administration (LISA) vs. INSURE

- Evidence: Meta-analysis of 3 RCTs (n=426) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)
- Results: LISA compared with INSURE reduced the risk of BPD/death.
- Treatment Effect: Relative Risk 0.63 (95% CI 0.42–0.93)
- Number Needed to Treat: 12 (95% CI 6–66)

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Abbreviations

ACS	Antenatal corticosteroids
BPD	bronchopulmonary dysplasia
CI	confidence interval
CPAP	continuous positive airway pressure
ELBW	extremely low birth weight
FRC	functional residual capacity
GA	gestational age
INSURE	intubation, surfactant administration, extubation
IPPV	intermittent positive pressure ventilation
LISA	less invasive surfactant administration
NNT	number needed to treat
PEEP	positive end expiratory pressure
PMA	post-menstrual age
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SI	sustained inflation
VLBW	very low birth weight

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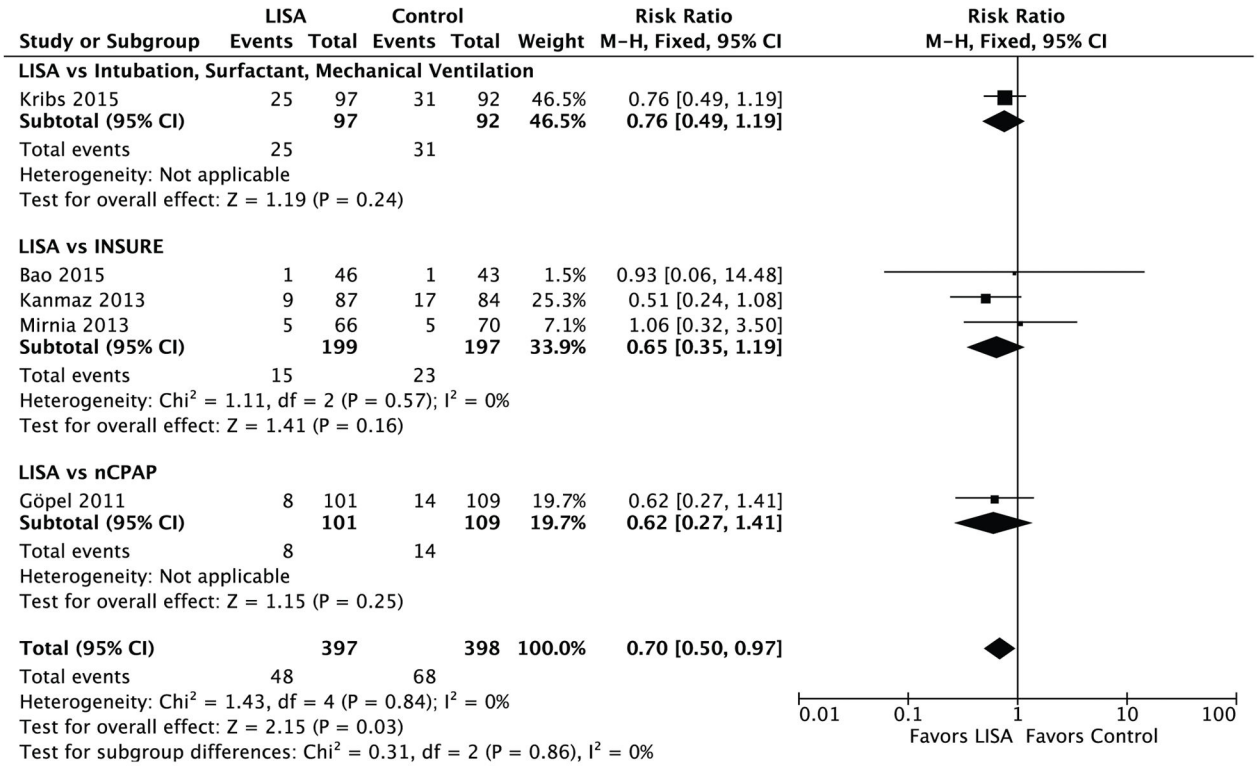

Figure 1.

Forrest plot for the outcome of BPD among survivors, comparing less invasive surfactant administration (LISA) versus control therapy in extremely preterm infants.

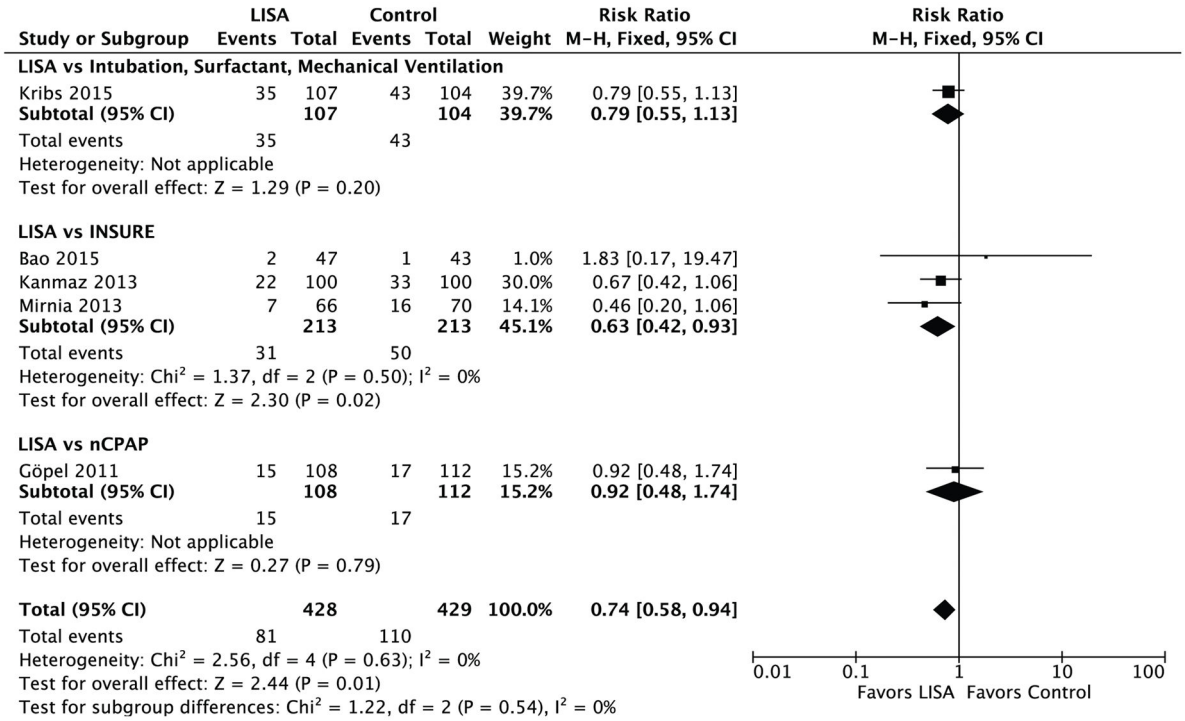

Figure 2.

Forrest plot for the outcome of death or BPD, comparing less invasive surfactant administration (LISA) versus control therapy in extremely preterm infants.

Table 1

Published randomized trials comparing SI with IPPV in extremely preterm infants

Study	Population	Comparison	Primary outcome	Comments
Lindner 2005 (36)	61 infants 25–28 $^{6/7}$ weeks GA	Up to three SI (20–30 cm H_2O X15 seconds) vs. IPPV Both via NP tube	Intubation at 48 HOL: SI (61%) vs. IPPV (70%), OR 0.68 (95 % CI 0.23–1.97)	Closed early for slow recruitment; under powered to detect a significant difference in primary outcome rates
Harling 2005 (35)	52 infants <31 weeks GA	One SI (25–30 cm H_2O X5 seconds) vs. IPPV (2 second inflation), via facemask or ETT	Cytokine concentrations from BAL at 12 hours of life: no significant differences between groups	Minimal treatment difference between groups Non-clinical primary outcome
te Pas 2007 (37)	207 infants 25–32$^{6/7}$ weeks GA	Up to two SI (20–25cm H_2O X10 seconds) with PEEP via NP tube vs. IPPV without PEEP via facemask	Intubation within 72 HOL: SI (37%) vs. IPPV (51%), OR 0.57 (95% CI 0.32–0.98)	No PEEP during IPPV for the control group, Different devices and interfaces used between groups
Lista 2015 (38)	291 infants 25–28$^{6/7}$ weeks GA	Up to two prophylactic SI (25 cm H_2O X15 seconds) via facemask vs. nasal CPAP with subsequent resuscitation per NRP guidelines	Intubation within 72 HOL: SI (53%) vs. CPAP (65%), OR 0.62 (95% CI 0.38–0.99)	Infants received prophylactic SI, regardless of respiratory status after birth
Jiravisitkul 2017 (39)	81 infants 25–32 weeks GA	Up to two SI (25 cm H_2O X15 seconds) via facemask vs. IPPV with PEEP via facemask	Mean FiO_2 at 10 minutes after birth: SI (0.28, 95% CI: 0.26–39) vs. control (0.47, 95% CI: 0.43–0.52), p<0.001	Proximal primary outcomes. Heart rate and pulse oximetry in first 10 minutes and delivery room intubation: no significant differences between groups

Abbreviations: BAL: bronchoalveolar lavage, BPD: bronchopulmonary dysplasia, CI: confidence interval, CPAP: continuous positive airway pressure, GA: gestational age, HOL: hours of life, IPPV: intermittent positive pressure ventilation, NRP: neonatal resuscitation program, OR: odds ratio, PEEP: positive end expiratory pressure, SI: sustained inflation

Table 2

Published randomized trials comparing low versus high FiO_2 during delivery room stabilization

Author	Population	Comparison	Primary outcome	Comments
Lundstrøm, 1995 (46)	70 infants <33 weeks GA	Initial FiO_2 21% vs. 80%, titrated clinically by response in HR.	Cerebral blood flow (measured by xenon clearance) at 2 HOL higher in low oxygen group (median 15.9 vs. 12.3 ml/100g/min), p<0.0001	FiO2 titrated based on HR, not SpO_2. Secondary outcome: No significant difference in supplemental O_2 at 28 days
Harling, 2005 (47)	52 infants <31 weeks GA	FiO_2 50% vs. 100%	Cytokine concentrations in BAL collected at 12 HOL: no significant differences	Secondary outcome: No significant difference in survival without BPD
Wang, 2008 (48)	41 infants 23–$31^{6/7}$ weeks GA	Initial FiO_2 21% vs. 100%, titrated per protocol	SpO_2 values during stabilization. SpO_2 significantly lower in 21% FiO_2 group from 2–10 MOL.	Secondary outcome: No significant difference in supplemental O_2 at 36 weeks PMA
Vento, 2009 (49)	78 infants 24–28 weeks GA	Initial FiO_2 30% vs. 90%, titrated per protocol	Neonatal death (<28 days) and BPD at 36 weeks PMA. No difference in neonatal death. Less BPD among survivors in low FiO_2 group (15% vs. 32%, p<0.05).	Secondary outcomes: Low FiO_2 group had significantly fewer days of supplemental O_2 and mechanical ventilation and lower markers of oxidative stress and inflammation
Rabi, 2011 (50)	106 infants ≤32 weeks GA	FiO_2: high (100% static), moderate (initial 100%, titrated), or low (initial 21%, titrated)	Time within target SpO_2 85–92% No differences in time to reach target SpO_2. Moderate group with greater proportion of time spent in target SpO_2 range than high group.	Secondary outcomes: no significant difference in BPD, death, or duration of mechanical ventilation
Armanian, 2012 (51)	32 infants 29–34 weeks GA	Initial FiO_2 30% vs. 100%, titrated per protocol	Outcomes reported: SpO_2 and HR per minute of life. More infants In 100% FiO_2 with HR>100 bpm at 2 MOL (94% vs. 50%, p=0.008)	Unclear primary outcome. All proximal outcomes (within first 5 MOL). Clinically relevant in-hospital outcomes not reported
Kapadia, 2013 (52)	88 infants 24–$34^{6/7}$ weeks GA	Initial FiO_2 21% versus 100%, titrated per protocol	Improved oxidative balance ratio (serum [BAP/TH]) at 1 HOL in 21% FiO_2 group (median 13 vs. 8, p<0.01)	Secondary outcome: 21% FiO_2 with less BPD (7% vs. 25%, p<0.05)
Rook, 2014 (53)	193 infants <32 weeks GA	Initial FiO_2 30% vs. 65%, titrated per protocol	BPD at 36 weeks PMA: no significant difference between groups, 24% (low FiO_2) vs. 17% (high FiO_2), p=0.15	Secondary outcomes: no differences in duration of mechanical ventilation or markers of oxidative stress
Oei (2017) (54)	287 infants <32 weeks GA	Initial FiO_2 21% versus 100%, titrated per protocol	Primary outcome (death or major disability at 2 years) not yet reported.	No significant difference in BPD between groups. Ancillary analysis of 119 enrolled infants revealed higher oxidative stress markers in the 100% FiO_2 group (91)

Abbreviations BAL: bronchoalveolar lavage, BAP: biological antioxidant potential, BPD: bronchopulmonary dysplasia, BPM: beats per minute, FiO_2: fraction of inspired oxygen, GA: gestational age, HOL: hour(s) of life, HR: heart rate, MOL: minute(s) of life, PMA: post-menstrual age, SpO_2 oxygen saturation (pulse oximetry), TH: total hydroperoxide