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Sustained Inflation vs Standard Resuscitation for Preterm Infants
A Systematic Review and Meta-analysis

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Supplemental content

IMPORTANCE Most preterm infants require respiratory support to establish lung aeration after birth. Intermittent positive pressure ventilation and continuous positive airway pressure are standard therapies. An initial sustained inflation (inflation time >5 seconds) is a widely practiced alternative strategy.

OBJECTIVE To conduct a systematic review and meta-analysis of sustained inflation vs intermittent positive pressure ventilation and continuous positive airway pressure for the prevention of hospital mortality and morbidity for preterm infants.

DATA SOURCES MEDLINE (through PubMed), Embase, the Cumulative Index of Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials were searched through June 24, 2019.

STUDY SELECTION Randomized clinical trials of preterm infants born at less than 37 weeks' gestation that compared sustained inflation (inflation time >5 seconds) vs standard resuscitation with either intermittent positive pressure ventilation or continuous positive airway pressure were included. Studies including other cointerventions were excluded.

DATA EXTRACTION AND SYNTHESIS Two reviewers assessed the risk of bias of included studies. Meta-analysis of pooled outcome data used a fixed-effects model specific to rarer events. Subgroups were based on gestational age and study design (rescue vs prophylactic sustained inflation).

MAIN OUTCOMES AND MEASURES Death before hospital discharge.

RESULTS Nine studies recruiting 1406 infants met inclusion criteria. Death before hospital discharge occurred in 85 of 736 infants (11.5%) treated with sustained inflation and 62 of 670 infants (9.3%) who received standard therapy for a risk difference of 3.6% (95% CI, −0.7% to 7.9%). Although analysis of the primary outcome identified important heterogeneity based on gestational age subgroups, the 95% CI for the risk difference included 0 for each individual gestational age subgroup. There was no difference in the primary outcome between subgroups based on study design. Sustained inflation was associated with increased risk of death in the first 2 days after birth (risk difference, 3.1%; 95% CI, 0.9%-5.3%). No differences in the risk of other secondary outcomes were identified. The quality-of-evidence assessment was low owing to risk of bias and imprecision.

CONCLUSIONS AND RELEVANCE There was no difference in the risk of the primary outcome of death before hospital discharge, and there was no evidence of efficacy for sustained inflation to prevent secondary outcomes. These findings do not support the routine use of sustained inflation for preterm infants after birth.

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Almost all very preterm infants require support to achieve lung aeration immediately after birth. The current standard practice is to provide intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure for infants with apnea and continuous positive airway pressure (CPAP) for spontaneously breathing infants who require respiratory support.[1] The optimal inflation time during IPPV to aerate the newborn lung after birth is unknown because airway resistance is higher in the presence of fetal fluid compared with air. Strategies to overcome this resistance include using higher pressures or longer inflation times.[2] Sustained inflation (SI), in which an inflating pressure is held for a prolonged duration greater than 5 seconds,[1] is an alternative approach to clear lung liquid and aerate the newborn lung.

Preclinical studies have demonstrated that SI leads to rapid and homogenous lung aeration.[3,4] In preliminary observational studies, preterm infants treated with SI experienced improved short-term outcomes, such as less frequent delivery room intubation and less exposure to mechanical ventilation in the first 72 hours of life compared with historical controls.[5-7] A recent Cochrane systematic review of 8 randomized clinical trials enrolling 941 infants found no evidence of benefit for SI for the primary outcome of mortality or for important secondary clinical outcomes.[8]

The recently completed Sustained Aeration of Infant Lungs (SAIL) randomized clinical trial (RCT) was the largest trial to date, to our knowledge, designed to compare SI with IPPV on the composite outcome of bronchopulmonary dysplasia or death at 36 weeks' postmenstrual age among extremely preterm infants.[9] The SAIL trial included more extremely preterm infants than previous trials and unexpectedly showed a higher rate of death in the first 2 days after birth in the experimental group. It was important to perform this systematic review to include the SAIL trial results and to investigate for evidence of differential treatment outcomes based on specified gestational age (GA) subgroups. The primary objective was to determine the effectiveness of SI vs standard resuscitation for the outcome of mortality prior to hospital discharge among preterm infants enrolled in RCTs.

Key Points

Question Is sustained inflation a more effective intervention than standard intermittent positive pressure ventilation or continuous positive airway pressure for preterm infants who require respiratory support after birth?

Findings In this systematic review and meta-analysis, sustained inflation was associated with a similar risk of in-hospital mortality compared with standard therapy. Sustained inflation was associated with an increased risk of mortality in the first 2 days compared with standard therapy, and there were no differences in the risk of any other secondary outcomes.

Meaning These results do not support the use of sustained inflation after birth to improve outcomes for preterm infants.

Methods

This systematic review and meta-analysis followed the standard methods of the *Cochrane Handbook for Systematic Reviews of Interventions,* version 5.1.0[10] and the Cochrane Neonatal Review Group.[11] Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[12] The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; identifier CRD42019133858).

We conducted a comprehensive search of MEDLINE (through PubMed), Embase, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) using the search terms (sustained inflation) OR (sustained AND inflation). We used database-specific filters for preterm infants and RCTs as provided by the Cochrane Neonatal Group. We searched for ongoing or unpublished trials using ClinicalTrials.gov and the World Health Organization International Trials Registry and Platform, and we identified abstracts from the Pediatric Academic Society annual meetings from the available archived years (2014-2019) by searching for the key terms *sustained inflation* and *clinical trial*. The search was last conducted on June 24, 2019.

We included RCTs enrolling preterm infants younger than 37 weeks' gestation that compared SI (inflation time >5 seconds) vs standard resuscitation with either IPPV using inflation times of 5 seconds or less or CPAP. We excluded studies with cointerventions outside of SI between the control and intervention groups. Protocolized differences in respiratory devices between treatment groups were considered cointerventions based on the differential consistency in pressure delivery between devices[13] as well as emerging clinical evidence of the superiority of a T-piece device over a self-inflating bag to prevent pulmonary morbidity.[14,15] Observational studies, cluster RCTs, and quasi-RCTs were excluded.

The primary outcome was death during hospitalization. Secondary outcomes included cardiopulmonary resuscitation (chest compressions or epinephrine) in the delivery room (DR), intubation in the DR, death in the DR, death in the first 2 days of life, intubation and mechanical ventilation in the first 72 hours of life, surfactant administration in the first 72 hours of life, air leaks (pneumothorax or pulmonary interstitial emphysema), grade 3 or 4 intraventricular hemorrhage, bronchopulmonary dysplasia (as defined by primary trial), medical or surgical treatment for patent ductus arteriosus, stage 3 or higher retinopathy of prematurity, or requiring therapy in either eye.

Two of us (E.E.F. and A.B.t.P.) independently assessed titles and abstracts to determine eligibility of all studies identified in the search. Reviewers retrieved full-text versions of all potentially eligible articles and articles for which the abstract contained insufficient information to determine eligibility. Any differences were resolved through consensus.

For each included trial, the following details were collected: study authors, calendar years in which the trial was conducted, publication details, trial design, duration and completeness of follow-up, single site vs multisite and location(s) of study, informed consent approach (antenatal, retrospective, or combination), devices and interfaces used, definition of SI (number, peak pressures, or duration), definition of control therapy, details and demographic characteristics of trial participants, and details of outcomes reported. Data were abstracted from published trial protocols as available. We contacted the trial authors to request missing data when needed. In addition, all authors of eligible studies provided additional pooled mortality data (death before hospital discharge, death in the DR, and death in the first 2 days) stratified by the following groupings: 23 to 24 6/7 weeks' GA, 25 to 26 6/7 weeks' GA, 27 to 31 6/7 weeks' GA, and 32 to 36 6/7 weeks' GA.

Two of us (E.E.F. and A.B.t.P.) assessed the risk of bias at the study level using the Cochrane Collaboration tool.[10] Disagreements between the reviewers were resolved through consensus after discussion. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method[16] was used to assess the strength of evidence across studies for the primary outcome and for the following prespecified clinically relevant secondary outcomes: cardiopulmonary resuscitation in the DR, intubation in the first 72 hours, pneumothorax, grade 3 or 4 intraventricular hemorrhage, and bronchopulmonary dysplasia. Consistent with the GRADE method, the assessment of inconsistency was based on the relative treatment effects rather than absolute differences (ie, risk difference [RD]). When applicable, the importance of each outcome was assigned consistently with the rating of the International Liaison Committee on Resuscitation.[17]

Statistical Analysis

The primary meta-analysis was performed using a fixed-effects model because the limited degree of observed heterogeneity across trials supported the assumption of a common underlying treatment effect. A direct aggregate data meta-analysis was performed. The incidence and 95% CIs of each outcome were calculated for each study for each treatment group. For studies with zero events, exact CIs were calculated. Because events are rare, the approach of Böhning et al[18] was used to estimate RDs in both the aggregate and cumulative data meta-analyses. Mantel-Haenszel relative risk (RR),[19] with Sweeting correction of the reciprocal of the opposite group size applied to groups with 0 events,[20] was calculated for the primary outcome and specified secondary outcomes included in the GRADE assessment. Random-effects models with a Hartung-Knapp correction were used for confirmatory analyses for all outcomes. The Cochrane *Q* statistic and the Higgins I^2 index[21] were used to evaluate heterogeneity. All analyses were performed using Stata, version 15.1 software (StataCorp LLC).

We preplanned subgroup analyses based on prespecified GA subgroups for all mortality outcomes (death before hospital discharge, death in the DR, and death in the first 2 days of life). Because few studies enrolled infants aged 23 to 24 6/7 weeks, post hoc subgroup analyses using 2 GA groups (<27 weeks' GA and ≥27 weeks' GA) were also performed for the primary mortality outcome. We prespecified 2 additional subgroup analyses of all outcomes based on 2 elements of trial design. The first was study design, characterized as rescue vs prophylactic based on the type of support provided in the standard resuscitation control group. Studies were considered to use a rescue approach if the infants in the control group of those trials were treated with IPPV. Trials were designated prophylactic if the infants who were allocated to the control intervention and required respiratory support received CPAP with or without IPPV. A second additional subgroup analysis compared SI defined as 15 seconds or more with SI defined as less than 15 seconds.

Results

The search yielded 129 original references. Full-text reviews were performed for 41 studies, and 9 studies[9,22-29] of 1406 infants were included in this review (eFigure 1 in the Supplement). Published study protocols for 3 included trials were also reviewed.[30-32]

One trial was excluded because SI was defined as 5 seconds or less.[33] Four trials were excluded on the basis of a trial design that allowed for cointerventions in addition to SI. In the trial by te Pas and Walther,[34] SI was part of a package of interventions that included DR CPAP, a T-piece device that generates positive end-expiratory pressure, and a novel nasopharyngeal interface. Infants in the control group were treated with IPPV without positive end-expiratory pressure or CPAP using a self-inflating bag and face mask. The trial by El-Chimi et al[35] and the registered Sustained Lung Inflation of Preterms trial[36] were excluded based on protocolized differences in respiratory devices between treatment groups, with a T-piece device in the intervention group and a self-inflating bag used for the control group. Last, 1 excluded trial compared continuous vs coordinated chest compressions.[37]

Characteristics of Study Design

There were important differences between trials with regard to the number and GA of included participants and the study design (**Table**).[9,22-29] In most studies, antenatal consent was obtained for infant participation, increasing the risk of recruitment of a nonrepresentative study population and limited generalizability.[38] The studies by Ngan et al[28] and Hunt et al[29] used a retrospective consent approach, in which the parents were approached for informed consent after the infants had received the randomized study intervention. In the multisite study by Kirpalani and colleagues,[9] a combination of antenatal and retrospective consent was used based on ethical approvals at each site.

Four trials[7,9,28,29] used a rescue approach, in which the infants in the control group received IPPV. The remaining trials used a prophylactic approach. The pressures used during SI varied across studies from 10 to 30 cm H_2O, and the duration of SI ranged from 10 to 20 seconds. In all trials, inflations of 15 seconds or greater were provided to at least some of the infants allocated to receive SI. In 1 RCT only, 1 SI was delivered,[27] while the remaining trial designs allowed for up to 2 to 3 SIs. Treatment provided to infants in the control group varied across studies and included IPPV, "inflation breaths," CPAP, or "routine resuscitation."

Assessment of Potential Sources of Bias

The assessment of potential sources of bias is presented in eTable 1 in the Supplement. As noted, many studies obtained

Table. Characteristics of Included Studies

Source	Setting	Gestational Age, wk	Infants, No.	Time of Consent	Rescue Approach[a]	SI Intervention	Control Intervention	Primary Outcome
Lindner et al,[22] 2005	Single site	25-28 6/7	61	Antenatal	Yes	≤3 SIs, 15 s each; 20, 25, and 30 cm H_2O via ventilator and NP tube	IPPV, initial settings 20/4-6 cm H_2O via ventilator and NP tube	Treatment failure requiring mechanical ventilation within 48 h
Lista et al,[23] 2015	Multisite	25-28 6/7	291	Antenatal	No	≤2 SIs, 15 s each; 25 cm H_2O via TPR	CPAP 5 cm H_2O with or without IPPV via TPR	Mechanical ventilation in first 72 h of life
Jiravisitkul et al,[24] 2017	Single site	25-32	81	Antenatal	No	≤2 SIs, 15 s each; 25 cm H_2O via TPR	CPAP 6 cm H_2O; IPPV, initial settings 15-20/5 cm H_2O via TPR	FiO_2, HR, and SpO_2 during resuscitation; FiO_2 at 10 min of life, DR intubation
Schwaberger et al,[25] 2015	Single site	28-33 6/7	40	Antenatal	No	≤3 SIs, 15 s each; 30 cm H_2O via TPR	CPAP 5 cm H_2O with or without IPPV via TPR	Change in CBV and cTOI
Mercadante et al,[26] 2016	Single site	34-36 6/7	185	Antenatal	No	≤2 SIs, 15 s each; 25 cm H_2O via TPR	NRP, starting with initial steps, respiratory support via TPR	Need for respiratory support
Abd El-Fattah et al,[27] 2017	Single site	<32	100	Antenatal	No	1 SI, 4 definitions used: 10-20 s, 15-20 cm H_2O via TPR	CPAP 5 cm H_2O, IPPV if needed via TPR	DR intubation
Ngan et al,[28] 2017	Single site	23-32 6/7	162	Postnatal	Yes	≤2 SIs: 24 cm H_2O for 20 s, 24 cm H_2O for 10-20 s via TPR	IPPV, initial settings 24/6 cm H_2O via TPR	BPD at 36 wk PMA
Hunt et al,[29] 2019	Single site	<34	60	Postnatal	Yes	≤2 SIs, 15 s each; 25 cm H_2O via TPR	≤2 Sequences of 5 inflations, 2-3 s each, initial settings 25/5 cm H_2O via TPR	Minute volume in first minute of ventilation
Kirpalani et al,[9] 2019	Multisite	23-26 6/7	426	Antenatal and postnatal, varied by site	Yes	≤2 SIs, 15 s each; 20 cm H_2O and 25 cm H_2O via TPR	IPPV, initial settings 20/5-7 cm H_2O via TPR	BPD or death at 36 wk PMA

Abbreviations: BPD, bronchopulmonary dysplasia; CBV, cerebral blood volume; CPAP, continuous positive airway pressure; cTOI, cerebral tissue oxygenation index; DR, delivery room; FiO_2, fraction of inspired oxygen; HR, heart rate; IPPV, intermittent positive pressure ventilation; NP, nasopharyngeal; NRP, neonatal resuscitation program; PMA, postmenstrual age; SI, sustained inflation; SpO_2, oxygen saturation as measured by pulse oximetry; TPR, T-piece resuscitator.

[a] Rescue approach: infants had to be deemed to require positive pressure ventilation to be enrolled.

informed consent antenatally, increasing the risk of a nongeneralizable population. Three studies were considered to have an unclear risk of selection bias because the method of generating the random sequence was not specified. In the trials by Ngan et al[28] and Hunt et al,[29] randomization envelopes were opened prior to the determination of eligibility for the trial, increasing the risk of selection bias related to inadequate allocation concealment. All RCTs were considered to be at high risk of performance bias because the caregivers were not blinded, but this factor did not introduce a serious risk of bias for the assessment of the primary outcome of hospital-based mortality. Three RCTs reported a substantial number of postrandomization exclusions. In the trial by Kirpalani et al,[9] these exclusions were distributed equally between treatment groups, while there were more infants in the SI group who were excluded after randomization in the trial by Ngan et al.[28] The allocation of infants excluded after randomization was not reported by Jiravisitkul and colleagues.[24] In that trial, the number of infants in the control group (n = 38) did not reach the target (n = 40), although the overall study recruitment goal was met. Early trial closure occurred in the trials of Lindner and colleagues[22] (for poor recruitment and projected futility) and Kirpalani et al[9] (for increased risk of the prespecified safety outcome of death in the first 48 hours after birth). We did not evaluate funnel plot asymmetry to assess for publication bias because fewer than 10 trials were included in this review.[10]

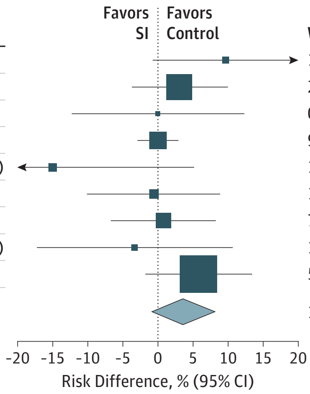
Primary Outcome: In-Hospital Mortality

A total of 9 studies were included in the primary meta-analysis. Death before hospital discharge occurred in 85 of 736 infants (11.5%) treated with SI and 62 of 670 infants (9.3%) who received standard therapy for an RD of 3.6% (95% CI, −0.7% to 7.9%) and an RR of 1.16 (95% CI, 0.86-1.57) (**Figure 1**; eFigure 2 in the Supplement). Heterogeneity of 17% was found in the RD model and 0% in the RR model. Confirmatory analyses using random-effects models produced similar estimates, with I^2 statistics of 0% for both RD and RR. Cumulative meta-analysis for the primary outcome (**Figure 2**) demonstrates a consistent point estimate favoring the control intervention.

Figure 3A shows the deaths during hospitalization by GA subgroups. The combined RD estimates were highest among infants of 23 to 24 6/7 weeks' GA (RD, 10.3%; 95% CI, −4.3% to 24.8%) and decreased to 0.0% (95% CI, −0.2% to 0.3%) among infants of 32 to 36 6/7 weeks' GA. The Mantel-Haenszel *Q* statistic for heterogeneity showed important differences between GA subgroups (Q = 15.9, df = 3; P < .001). In

Figure 1. Fixed-Effects Meta-analysis of Risk Difference of Primary Outcome, Death During Hospitalization

Source	SI, No./Total No.	Control, No./Total No.	Risk Difference, % (95% CI)	Weight, %
Lindner et al,[22] 2005	3/31	0/30	9.7 (-0.7 to 20.1)	1.1
Lista et al,[23] 2015	17/148	12/143	3.1 (-3.8 to 10.0)	24.3
Schwaberger et al,[25] 2015[a]	0/20	0/20	0.0 (-12.3 to 12.3)	0.5
Mercadante et al,[26] 2016[a]	0/93	0/92	0.0 (-2.9 to 2.9)	9.8
Abd El-Fattah et al,[27] 2017	8/80	5/20	-15.0 (-35.1 to 5.1)	1.8
Jiravisitkul et al,[24] 2017	2/43	2/38	-0.6 (-10.1 to 8.9)	1.9
Ngan et al,[28] 2017	5/76	5/86	0.8 (-6.7 to 8.2)	7.5
Hunt et al,[29] 2019	2/30	3/30	-3.3 (-17.3 to 10.6)	1.0
Kirpalani et al,[9] 2019	48/215	35/211	5.7 (-1.8 to 13.2)	52.1
Overall estimate Heterogeneity: I^2 = 16.5%	85/736	62/670	3.6 (-0.7 to 7.9)	100

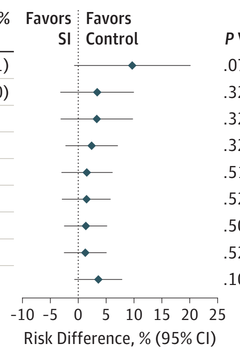


Study weights are indicated by the box sizes. Overall estimate and 95% CI are indicated by the diamond. SI indicates sustained inflation.

[a] Exact 95% CIs are shown.

Figure 2. Fixed-Effects Cumulative Meta-analysis of Risk Difference of Primary Outcome, Death During Hospitalization

Source	Risk Difference, % (95% CI)	*P* Value
Lindner et al,[22] 2005	9.7 (-0.7 to 20.1)	.07
Lista et al,[23] 2015	3.4 (-3.2 to 10.0)	.32
Schwaberger et al,[25] 2015	3.3 (-3.2 to 9.8)	.32
Mercadante et al,[26] 2016	2.4 (-2.3 to 7.1)	.32
Abd El-Fattah et al,[27] 2017	1.5 (-3.0 to 6.1)	.51
Jiravisitkul et al,[24] 2017	1.4 (-2.9 to 5.8)	.52
Ngan et al,[28] 2017	1.3 (-2.5 to 5.2)	.50
Hunt et al,[29] 2019	1.2 (-2.6 to 5.0)	.52
Kirpalani et al,[9] 2019	3.6 (-0.7 to 7.9)	.10



SI indicates sustained inflation.

post hoc subgroup analysis based on only 2 GA strata, there was no difference in the outcome of mortality before hospital discharge among either stratum (eFigure 3 in the Supplement). The results for the pooled analysis of the primary outcome based on the study design subgroups (rescue vs prophylactic) are shown in Figure 3B. Because SI lasting 15 seconds or more was provided to at least some participants in the SI group of all trials, subgroup analysis based on duration of SI (<15 seconds vs ≥15 seconds) was not performed.

Secondary Outcomes

Figure 4 shows the results for the fixed-effect meta-analysis combined RD for all of the secondary outcomes and using all possible studies for each outcome, ranging from 2 to 9 studies. Death in the first 2 days of life showed an increased risk with SI (RD, 3.1%; 95% CI, 0.9%-5.3%) but with moderate heterogeneity (I^2 = 48%). Stratification by the 4 GA subgroups (eFigure 4 in the Supplement) provided an explanation for this heterogeneity. The pooled RD was likely associated with the infants of 23 to 24 6/7 weeks' GA (RD, 11.9%; 95% CI, 3.3%-20.5%). Cumulative meta-analysis demonstrates a substantial association between the SAIL trial data and this outcome (eFigure 5 in the Supplement). Subgroup analysis for the outcome of mortality in the DR based on GA is shown in eFigure 6 in the Supplement. Analysis of secondary outcomes based on the study design subgroups is shown in eFigure 7 in the Supplement.

The GRADE Assessment of Evidence table for key prespecified outcomes is shown in eTable 2 in the Supplement, with fixed-effects and random-effects models for these outcomes in eTable 3 in the Supplement. The outcome of cardiopulmonary resuscitation in the DR is presented as individual components of chest compressions and epinephrine. The quality of data for specified outcomes was downgraded to low owing to risk of bias and imprecision.

Discussion

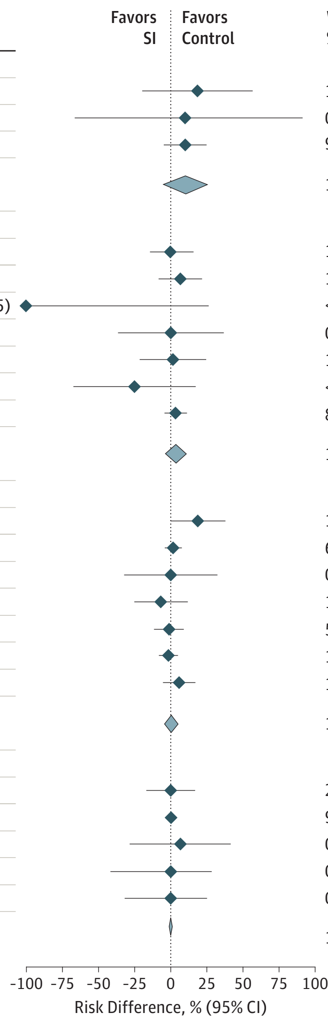
Lung aeration is essential for the successful transition to the extrauterine environment after birth, and almost all extremely preterm infants require respiratory support during this process. Only limited data inform the choice of inflation times and pressures used during positive pressure ventilation in the DR.[39] In this pooled analysis of 1406 preterm infants enrolled in 9 RCTs of SI compared with standard resuscitation, there was no significant difference in the risk of the primary outcome of death before hospital discharge. However, SI was associated with an increased risk of mortality in the first 2 days of life, especially in the least mature GA subgroup. There were no observed differences between SI and control therapy in the risk of any other specified secondary outcomes.

Previous observational studies and RCTs of SI provided limited but promising evidence favoring SI over IPPV.[2] The SAIL trial was the largest trial to date, contributing 30% of the infants included in this review.[9] The SAIL trial enrolled only the most extremely preterm infants (23-26 6/7 weeks' GA), a more immature population than in previous studies. The SAIL trial was closed early based on an interim, blinded, case-by-case clinical analysis that found an increased risk of death in the first 48 hours after birth among infants in the SI group. We therefore conducted this pooled analysis of SI trials (including SAIL) to examine for evidence of harm with SI, particularly among the most extremely preterm infants.

Figure 3. Subgroup Analysis of Risk Difference for Death During Hospitalization

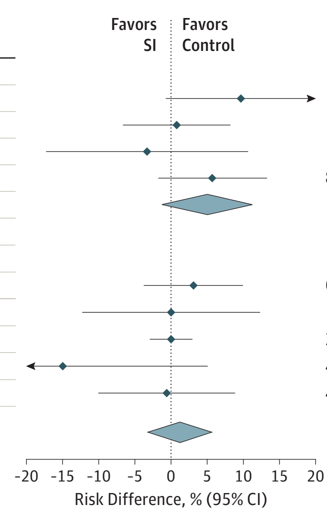
A Gestational age subgroups

Source	SI, No/ Total No.	Control, No./ Total No.	Risk Difference, % (95% CI)	Weight, %
23-24 6/7 wk				
Ngan et al,[28] 2017	2/7	1/10	18.6 (-19.7 to 56.9)	1.2
Hunt et al,[29] 2019	1/2	2/5	10.0 (-71.5 to 91.5)	0.2
Kirpalani et al,[9] 2019	28/76	20/75	10.2 (-4.6 to 24.9)	98.6
Overall estimate Heterogeneity, I^2 = 0.0%	31/85	23/90	10.3 (-4.3 to 24.8)	100
25-26 6/7 wk				
Lindner et al,[22] 2005[a]	0/15	0/17	0.0 (-14.4 to 15.6)	1.1
Lista et al,[23] 2015	12/52	9/55	6.7 (-8.3 to 21.8)	12.8
Abd El-Fattah et al,[27] 2017[a]	0/1	2/2	-100.0 (-100.0 to 26.5)	<0.1
Jiravisitkul et al,[24] 2017[a]	0/5	0/5	0.0 (-36.7 to 36.7)	0.1
Ngan et al,[28] 2017	2/15	2/17	1.6 (-21.5 to 24.6)	1.1
Hunt et al,[29] 2019	0/2	1/4	-25.0 (-67.4 to 17.4)	<0.1
Kirpalani et al,[9] 2019	20/139	15/136	3.4 (-4.5 to 11.2)	84.7
Overall estimate Heterogeneity, I^2 = 0.0%	34/229	29/236	3.7 (-3.2 to 10.6)	100
27-31 6/7 wk				
Lindner et al,[22] 2005[a]	3/16	0/13	18.8 (-0.4 to 37.9)	1.5
Lista et al,[23] 2015	5/96	3/88	1.8 (-4.0 to 7.6)	62.0
Schwaberger et al,[25] 2015[a]	0/6	0/6	0.0 (-32.4 to 32.4)	0.3
Abd El-Fattah et al,[27] 2017	8/79	3/18	-6.5 (-25.0 to 11.9)	10.4
Jiravisitkul et al,[24] 2017	1/32	1/23	-1.2 (-11.5 to 9.1)	5.4
Ngan et al,[28] 2017	1/46	2/55	-1.5 (-8.0 to 5.0)	18.6
Hunt et al,[29] 2019	1/17	0/15	5.9 (-5.3 to 17.1)	1.9
Overall estimate Heterogeneity, I^2 = 10.7%	19/292	9/218	0.5 (-3.8 to 4.8)	100
32-36 6/7 wk				
Schwaberger et al,[25] 2015[a]	0/14	0/14	0.0 (-16.8 to 16.8)	2.2
Mercadante et al,[26] 2016[a]	0/93	0/92	0.0 (-2.9 to 2.9)	96.2
Jiravisitkul et al,[24] 2017	1/6	1/10	6.7 (-28.5 to 41.8)	0.7
Ngan et al,[28] 2017[a]	0/8	0/4	0.0 (-41.8 to 28.5)	0.4
Hunt et al,[29] 2019[a]	0/9	0/6	0.0 (-31.9 to 25.1)	0.6
Overall estimate Heterogeneity, I^2 = 0.0%	1/130	1/126	0.0 (-0.2 to 0.3)	100



B Study design subgroups

Source	SI, No/ Total No.	Control, No./ Total No.	Risk Difference, % (95% CI)	Weight, %
Rescue				
Lindner et al,[22] 2005	3/31	0/30	9.7 (-0.7 to 20.1)	1.7
Ngan et al,[28] 2017	5/76	5/86	0.8 (-6.7 to 8.2)	12.2
Hunt et al,[29] 2019	2/30	3/30	-3.3 (-17.3 to 10.6)	1.7
Kirpalani et al,[9] 2019	48/215	35/211	5.7 (-1.8 to 13.2)	84.4
Overall estimate	58/352	43/357	5.0 (-1.4 to 11.4)	100
Heterogeneity, I^2 = 13.0%				
Prophylactic				
Lista et al,[23] 2015	17/148	12/143	3.1 (-3.8 to 10.0)	63.5
Schwaberger et al,[25] 2015[a]	0/20	0/20	0.0 (-12.3 to 12.3)	1.2
Mercadante et al,[26] 2016[a]	0/93	0/92	0.0 (-2.9 to 2.9)	25.7
Abd El-Fattah et al,[27] 2017	8/80	5/20	-15.0 (-35.1 to 5.1)	4.8
Jiravisitkul et al,[24] 2017	2/43	2/38	-0.6 (-10.1 to 8.9)	4.9
Overall estimate Heterogeneity, I^2 = 31.9%	27/384	19/313	1.2 (-3.4 to 5.7)	100



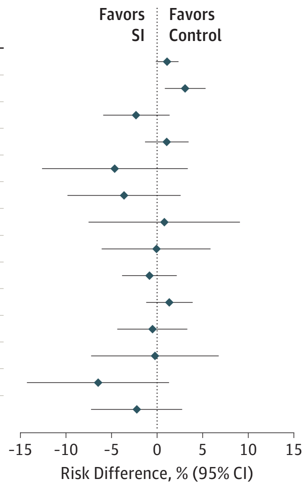
A, Gestational age subgroups. B, Study design subgroups. Overall estimate and 95% CI are indicated by the diamond. SI indicates sustained inflation.

[a] Exact 95% CIs are shown.

This study specifically includes preplanned subgroup analyses based on GA. We obtained aggregate data from all included trials to examine for differences in the mortality risk based on uniformly defined GA subgroups. Although there

Figure 4. Fixed-Effects Meta-analysis for Risk Difference of All Secondary Outcomes

Source	Studies, No.	SI, No./Total No.	Control, No./Total No.	Risk Difference, % (95% CI)	I^2, %
Died in DR	9	8/736	2/670	1.1 (-0.2 to 2.3)	0.0
Died in first 2 days	9	25/736	10/670	3.1 (0.9 to 5.3)	48.2
Chest compressions	2	12/291	17/291	-2.3 (-5.9 to 1.3)	30.3
Epinephrine in DR	2	6/291	4/297	1.1 (-1.3 to 3.4)	73.1
Intubation in DR	4	164/414	168/355	-4.6 (-12.7 to 3.4)	62.7
Intubation in first 72 h	6	312/592	313/528	-3.6 (-9.8 to 2.6)	0.0
Surfactant in DR	3	131/322	123/327	0.8 (-7.5 to 9.1)	0.0
Surfactant at any time	6	347/582	326/518	-0.1 (-6.1 to 5.9)	0.0
Pneumothorax	7	26/629	26/554	-0.8 (-3.9 to 2.2)	60.1
PIE	3	15/383	8/374	1.4 (-1.2 to 3.9)	0.0
Grade 3 or 4 IVH	8	54/643	61/578	-0.5 (-4.3 to 3.3)	6.1
BPD	8	199/544	205/489	-0.2 (-7.2 to 6.8)	27.6
PDA	6	155/454	166/388	-6.5 (-14.2 to 1.3)	41.4
ROP	7	69/586	80/514	-2.2 (-7.2 to 2.7)	68.2



BPD indicates bronchopulmonary dysplasia; DR, delivery room; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; PIE, pulmonary interstitial emphysema; ROP, retinopathy of prematurity; and SI, sustained inflation.

were no differences in the primary outcome for any subgroup, there was important heterogeneity between subgroups for this outcome, favoring control therapy in the least mature subgroup (23-24 6/7 weeks' GA) of infants, who experience high mortality event rates.

The cumulative meta-analysis demonstrates point estimates that consistently favored control therapy for the primary outcome of mortality prior to hospital discharge. Explanations for this finding are speculative. Sustained inflation may have exacerbated cardiorespiratory failure after birth in this vulnerable population by delaying initiation of effective ventilation, leading to end organ injury. Alternatively, because rapid lung inflation with SI can lead to regional lung overdistention and injury,[40] it is possible that SI as operationalized in the included RCTs contributed to volutrauma and acute lung injury among extremely preterm infants. However, there were no differences in air leaks or other secondary outcomes in pooled analysis to suggest a unified causal pathway for increased mortality.

Sustained inflation was associated with an increased risk of mortality in the first 2 days of life in pooled analysis, but this finding was not consistently evident in the cumulative meta-analysis prior to the addition of the SAIL trial data.[9] This finding may reflect the fact that the SAIL trial enrolled the largest number of the least mature infants and had higher event rates of early mortality than most other trials. Alternatively, it is possible that the increased mortality in the first 2 days of life among infants treated with SI in the SAIL trial was a chance finding, particularly because this end point was 1 of 34 prespecified secondary and safety outcomes assessed in that study.

Ultimately, the association of SI and IPPV with lung aeration, gas exchange, and volutrauma likely depends on how effectively the interventions are applied. Most of the included trials were pragmatic and did not include respiratory recordings to assess the actual pressures and volumes delivered. Although some preclinical studies found SI to be a superior approach to lung aeration, respiratory interventions in those studies were delivered via endotracheal tubes to anesthetized animals.[3,4] Study results may not apply to SIs delivered via face mask to preterm infants. Known technical impediments, such as mask leak and airway obstruction, reduce effective tidal volume delivery during face mask ventilation.[41-43] It is possible that there was diminished gas volume delivered for infants treated with both noninvasive SI and IPPV.

In addition, laryngeal closure impedes effective noninvasive ventilation.[44] In previous preterm studies, very little air volume entered the lung unless breathing occurred during SI.[45,46] Therefore, we performed a subgroup analysis based on study design for the likelihood of glottis opening with spontaneous breathing among enrolled infants. In the 4 rescue trials, all infants in the control group received IPPV, suggesting absent or insufficient respiratory effort and a closed glottis among enrolled infants. In the 5 prophylactic trials, infants in the control group could have received CPAP, which suggests that many enrolled participants had sufficient respiratory effort and therefore an open glottis. In this subgroup analysis, mortality favored the control in both the rescue and prophylactic trials, although the 95% CI included 0 for both subgroups.

Limitations

We acknowledge the limitations of our study. Only 9 available trials met the eligibility criteria, contributing to the imprecision of the results. However, the pooled analysis suggests that additional data from further trials would not demonstrate evidence of efficacy for SI for the critical outcome of in-hospital mortality. Although the number of included trials precluded the ability to conduct formal tests to assess for publication bias, our comprehensive search strategy included both published and unpublished sources to reduce this risk of bias. In addition, there were important differences between studies in the maturity of enrolled infants, definition of SI, and interventions applied in the control group. Subgroup analyses to account for some of these differences show little evidence of additional harm nor added benefit associated with SI.

Conclusions

This pooled analysis of 1406 preterm infants presents some evidence that favors standard resuscitation over SI for the outcome of death during hospitalization. Sustained inflation is associated with an increased risk of death in the first 2 days after birth, and there is no evidence of efficacy for SI to prevent other secondary outcomes. These findings do not support the routine use of SI for preterm infants after birth.

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