Sustained Lung Inflation at Birth for Preterm Infants: A Randomized Clinical Trial

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abstract

BACKGROUND: Studies suggest that giving newly born preterm infants sustained lung inflation (SLI) may decrease their need for mechanical ventilation (MV) and improve their respiratory outcomes.

METHODS: We randomly assigned infants born at 25 weeks 0 days to 28 weeks 6 days of gestation to receive SLI (25 cm H_2O for 15 seconds) followed by nasal continuous positive airway pressure (nCPAP) or nCPAP alone in the delivery room. SLI and nCPAP were delivered by using a neonatal mask and a T-piece ventilator. The primary end point was the need for MV in the first 72 hours of life. The secondary end points included the need for respiratory supports and survival without bronchopulmonary dysplasia (BPD).

RESULTS: A total of 148 infants were enrolled in the SLI group and 143 in the control group. Significantly fewer infants were ventilated in the first 72 hours of life in the SLI group (79 of 148 [53%]) than in the control group (93 of 143 [65%]); unadjusted odds ratio: 0.62 [95% confidence interval: 0.38–0.99]; P = .04). The need for respiratory support and survival without BPD did not differ between the groups. Pneumothorax occurred in 1% (n = 2) of infants in the control group compared with 6% (n = 9) in the SLI group, with an unadjusted odds ratio of 4.57 (95% confidence interval: 0.97–21.50; P = .06).

CONCLUSIONS: SLI followed by nCPAP in the delivery room decreased the need for MV in the first 72 hours of life in preterm infants at high risk of respiratory distress syndrome compared with nCPAP alone but did not decrease the need for respiratory support and the occurrence of BPD.

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WHAT'S KNOWN ON THIS SUBJECT: Sustained lung inflation and positive end-expiratory pressure would permit lung recruitment immediately after birth, improving lung mechanics and reducing the need for respiratory support. Previous clinical studies in preterm infants provided promising results but have some limitations.

WHAT THIS STUDY ADDS: This randomized controlled study found that prophylactic sustained lung inflation and positive end-expiratory pressure in the delivery room decreased the need for mechanical ventilation in the first 72 hours of life in preterm infants at high risk of respiratory distress syndrome.

The pathogenesis of bronchopulmonary dysplasia (BPD) in preterm infants is multifactorial, but the role of ventilator-induced lung injury is important.[1] Although the respiratory support of preterm infants with respiratory distress syndrome (RDS) has improved and new modes of mechanical ventilation (MV) have been developed, the incidence of BPD has remained high. An aspect of respiratory care of preterm infants that has not yet been thoroughly investigated is the support given in the delivery room immediately after birth. Lung protection should start in the delivery room where, from the first breaths, the preterm infant can be helped to clear lung fluid; to recruit the functional residual capacity (FRC); to avoid large tidal volumes; to avoid the continuous "opening and closing" of the alveoli by delivering positive end-expiratory pressure (PEEP); and to verify the need for surfactant replacement.[2,3]

Recent studies[2,4–6] have investigated the effect that the sustained lung inflation (SLI) procedure has in preterm infants on avoiding the need for MV. This strategy would permit lung recruitment immediately after birth through delivery of brief peak pressure to the infant airways via a nasopharyngeal tube or mask, allowing preterm infants to achieve FRC. The application of PEEP helps to avoid lung collapse at the end of the expiration. SLI and PEEP seem to have an additive effect on adequate FRC formation by permitting optimal gas exchange, improving lung mechanics, and reducing the need for respiratory support.[7]

This technique has been proven to be more effective than intermittent mandatory ventilation (IMV) in improving FRC in the asphyxiated term newborn.[8,9] Lindner et al[4] treated preterm infants by using SLI in the delivery room, with no significant decreases in the MV rate or adverse effects compared with treatment with nasal IMV. More recently, te Pas et al[5] treated preterm infants with repeatable SLI maneuvers and found a decrease in the need for MV at 72 hours of life and moderate/severe BPD compared with treatment in the delivery room with a self-inflating bag. These results are in agreement with the findings of another study from the same group that found a synergistic effect of SLI and PEEP (delivered by nasal continuous airway pressure [nCPAP]) in achieving and maintaining of an FRC improvement in an animal model.[7] Moreover, Lista et al[6] recently reported that SLI followed by the delivery of early nCPAP is effective in reducing the need for MV and the occurrence of BPD in survivors compared with nCPAP alone. However, previous studies have some relevant limitations: the study by Lindner et al[4] was stopped because of slow patient recruitment when 55% of estimated patients were enrolled; in the study by te Pas et al,[5] infants in the control group were assisted by using a self-inflating bag and mask that supplies only minimal PEEP; and the Lista et al[6] study was not a randomized controlled trial. Therefore, we planned the present randomized controlled SLI trial in which we compared the application of prophylactic SLI followed by nCPAP with nCPAP alone in the delivery room. The basis of our hypothesis was that the use of SLI combined with early nCPAP shortly after birth would reduce the need for MV and would improve respiratory outcome in preterm infants at high risk of RDS.

METHODS

Study Design

This national, multicenter trial performed in perinatal centers was approved by the ethics committee at each center. Infants were eligible for inclusion in the study if they were between the ages of 25 weeks 0 days and 28 weeks 6 days at the time of birth. This age group was chosen because it is at high risk of RDS. Exclusion criteria were the presence of major congenital malformations (ie, congenital heart, cerebral, lung, abdominal malformations), fetal hydrops, and lack of parental consent. Written and oral information were offered to all parents before the birth during antenatal controls if there was a risk of preterm delivery or at the mother's hospital admission in case of sudden delivery. Informed written consent was signed by both the parents, and sufficient time was allowed for consent.

Randomization

Infants were assigned immediately after birth before the first breath to receive either SLI maneuvers and nCPAP or nCPAP alone in a 1:1 ratio in permuted blocks of variable size. Randomization was stratified according to center and gestational age (25 or 26 weeks and 27 or 28 weeks). Group assignment was contained in sequentially numbered, sealed, opaque envelopes that were prepared by an independent statistician. The study was not blinded, and the staff performing the study also cared for the infants later on. The decision to start MV was made by clinicians other than the investigators involved in the study according to specific guidelines, and researchers assessing study end points were blinded to the nature of the study treatments.

Study Intervention

Infants in the SLI group underwent the following approach: after oropharyngeal and nasal suctioning, a pressure-controlled (25 cm H_2O) inflation was sustained for 15 seconds, followed by the delivery of 5 cm H_2O CPAP, using a neonatal mask and a T-piece ventilator (Neopuff Infant Resuscitator, Fisher & Paykel, Auckland, New Zealand). A peak pressure of 25 cm H_20 was chosen because this level had been shown to be effective and safe in previous studies,[4,5] and an inflation duration of 15 seconds was used because it had

been well tolerated and followed by a greater FRC in previous clinical and experimental studies.[2,3] The flow rate was set at 8 to 10 L/min before resuscitation and was not changed during resuscitation. Patients were observed for the next 6 to 10 seconds to evaluate their cardiorespiratory function. If respiratory failure persisted (ie, apnea, gasping) and/or the heart rate was >60 and <100 beats/min despite CPAP, the SLI maneuver (again 25 cm H_2O for 15 seconds) was repeated. If the heart rate remained >60 and <100 beats/min after the second SLI maneuver, the infant was resuscitated following the guidelines of the American Academy of Pediatrics.[10] Infants in the control group were treated with nCPAP at 5 cm H_2O and were assisted according to the guidelines of the American Academy of Pediatrics.

Infants in both groups who were not intubated in the delivery room were transferred to the NICU on nCPAP at 5 cm H_2O with a fraction of inspired oxygen (F_{IO_2}) of 0.21 to 0.40 (in agreement with local protocols).

Criteria for Starting MV

In the delivery room, infants were started on MV if they had a heart rate <60 beats/min despite proper positive pressure ventilation, in agreement with the guidelines of the American Academy of Pediatrics.[10] In the NICU, infants were started on MV when the pH was <7.20 with P_{aCO_2} >65 mm Hg, or P_{aO_2} <50 mm Hg with F_{IO_2} ≥0.50, after surfactant treatment, or if infants had frequent episodes of apnea (>4 episodes in 1 hour or >2 episodes requiring bag-and-mask ventilation) despite adequate nCPAP (5–7 cm H_2O) delivery and oxygenation. MV was set to maintain a P_{aCO_2} of 55 to 65 mm Hg and 88% to 95% pulse oxygen saturation.

Other Aspects of Respiratory Support

Infants with an F_{IO_2} ≥0.40 to maintain an adequate pulse oxygen saturation were treated with surfactant (200 mg/kg; Curosurf, Chiesi Farmaceutici SpA, Parma, Italy) followed by the re-institution of nCPAP as soon as their vital signs were satisfactory. All infants who were ventilated were treated with surfactant. Additional doses of surfactant (100 mg/kg) were given to infants at the discretion of the attending neonatologist.

Infants were extubated, after a loading dose of caffeine citrate (20 mg/kg), when they met all of the following criteria: F_{IO_2} <0.40, P_{aCO_2} <65 mm Hg with a pH >7.20, mean arterial pressure <7 cm H_2O, hemodynamic stability, and the absence of clinically significant patent ductus arteriosus.

Outcomes

The primary end point of the study was MV within the first 72 hours of life. We chose this variable as the primary outcome because of the crucial role that ventilator-induced lung injury plays in the pathogenesis of BPD[1] and because its early occurrence is less affected by later causes of respiratory impairment (ie, pulmonary infections). Moreover, this primary end point allows us to maintain similarity with the main trial conducted earlier on this issue.[5]

Prespecified secondary end points were MV in the first 3 hours of life, highest F_{IO_2}, duration of nCPAP, need and duration of bilevel nCPAP, nasal IMV, MV (synchronized intermittent MV, synchronized intermittent positive pressure ventilation, pressure support ventilation with or without volume guarantee) or high-frequency ventilation, duration of hospitalization, need and number of doses of surfactant, occurrence of RDS, BPD, and mortality.

The diagnosis of RDS was based on the occurrence of typical signs (need for oxygen supplementation, tachypnea, intercostal retractions, and grunting)[11] and appearances on chest radiographs (decreased lung expansion, reticulogranular pattern of the lung, and air bronchograms)[12] and the exclusion of other causes of respiratory failure. Diagnosis of BPD was based on the need for supplemental oxygen to maintain adequate oxygenation at 36 weeks of postconceptional age in surviving infants.[13]

Other Collected Data

The following data were recorded for each infant: gestational age, birth weight, birth weight <10th percentile for gestational age, gender, singleton or twin, occurrence of pneumothorax, pharmacologic treatment and surgical closure of patent ductus arteriosus, intraventricular hemorrhage,[14] periventricular leukomalacia,[15] retinopathy of prematurity,[16] necrotizing enterocolitis,[17] sepsis, length of stay in hospital, and mortality.

The maternal variables examined included antenatal steroid treatment, type of delivery, placental abruption, hypertensive disorders, prolonged premature rupture of membranes >18 hours, and clinical chorioamnionitis (defined as the presence of fever with ≥1 of the following: maternal leukocytosis >15 000/ mm^3, uterine tenderness, fetal tachycardia, or foul-smelling amniotic fluid).

Statistical Analysis

On the basis of data from a previous study[18] in which some Italian centers participated, we hypothesized that the SLI maneuver might decrease the need for MV during the first 72 hours of life from 35% to 20%. We calculated that we needed to enroll 138 newborns in each group to detect this difference as statistically significant with 80% power at the 0.05 level.

Data analysis was performed according to the intention-to-treat principle. Baseline characteristics were compared by using the χ^2 test for categorical variables and the *t* test for continuous variables with

Gaussian distribution. Odds ratios with 95% confidence interval (CIs) were estimated according to a logistic model for treatment comparisons of the main dichotomous outcomes between the 2 study groups. The crude cumulative incidence of BPD, retinopathy of prematurity, and median duration of hospital stay were calculated according to Kalbfleisch and Prentice[19] considering death due to any cause as a competing risk. For time-to-event outcomes, hazard ratios with 95% CIs were estimated with the Fine and Gray model, in the presence of competing risks, and with the Cox proportional hazards model otherwise. The likelihood ratio test was used to quantify the statistical significance of all coefficients. The Wilcoxon rank-sum test was used to compare continuous outcomes with highly skewed distribution. As sensitivity analyses, the estimates of the treatment effect were also adjusted with the use of statistical models that included terms for gestational age and study center (results from centers that enrolled <10 infants were combined in the same stratum). Subgroup analyses were performed with exploratory intent on the basis of the test for interaction. All statistical tests were 2-sided, and P values ≤.05 were considered to be statistically significant. No adjustment for multiple comparisons was made. Statistical analyses were performed by 1 of the authors (L.B.) using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

The numbers of infants deemed eligible for the study and the numbers randomly assigned to receive the SLI procedure or standard assistance in the delivery room are shown in Fig 1. A total of 294 infants were enrolled between October 1, 2011, and January 31, 2013. Three infants (1 erroneously randomized to treatment twice and 2 stillborn) were excluded from the intention-to-treat population. All patients were followed up to their first discharge home, and no violations of criteria for starting MV were reported. The baseline characteristics of infants at birth and of their mothers were similar in the 2 groups with the exception of male gender, which was more frequent in the SLI group (45% vs 58%; P = .04) (Table 1).

In the control group compared with the SLI group, the unadjusted odds ratio for the primary outcome of MV within the first 3 days of life was 0.62 (95% CI: 0.38–0.99; P = .04) (Table 2). The comparison was not substantially changed by adjustment using logistic regression, as described.

The use of noninvasive respiratory supports (bilevel nCPAP, nasal IMV) and MV (synchronized intermittent MV/synchronized intermittent positive pressure ventilation/pressure support ventilation, high-frequency ventilation) at any time during the hospital stay was not affected by the SLI procedure, as evidenced by their unadjusted and adjusted odds ratios. Similarly, the duration of noninvasive support and MV, as well as the need and number of doses of surfactant, did not differ in the 2 treatment groups (Tables 2 and 3).

At 36 weeks' gestational age, 35% (n = 50) of surviving infants in the control group had BPD compared with 39% (n = 57) in the SLI group (unadjusted hazard ratio: 1.17 [95% CI: 0.80–1.71]). Twelve infants in the control group and 17 in the SLI group died during the study (cumulative mortality during the in-hospital stay: 8% vs 11%; P = .39) (Table 2).

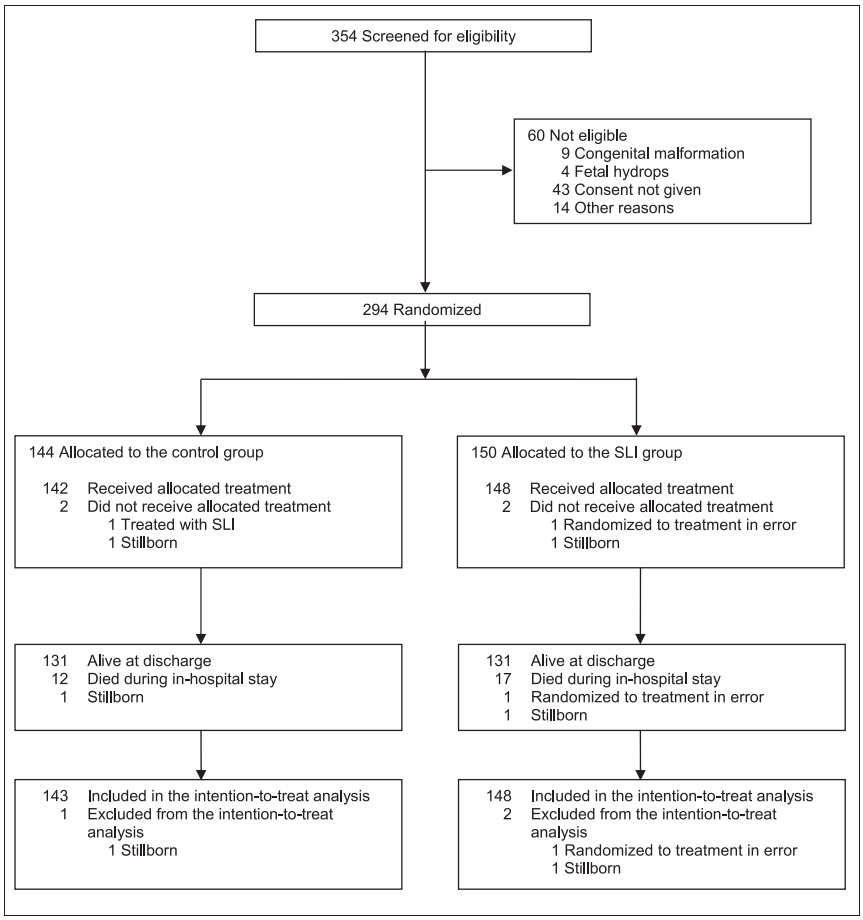

FIGURE 1
Consolidated Standards of Reporting Trials diagram.

TABLE 1 Baseline Clinical Characteristics of the Infants and Their Mothers

Characteristic	Control Group (n = 143)	SLI Group (n = 148)
Mothers		
Antenatal steroids	125 (87)	134 (91)
Cesarean delivery	116 (81)	120 (81)
Placental abruption	15 (10)	21 (14)
Hypertension disorders	42 (29)	35 (24)
pPROM	39 (27)	39 (26)
Chorioamnionitis	14 (10)	19 (13)
Other complications	43 (30)	48 (32)
Infants		
Gestational age, mean ± SD, wk	26.8 ± 1.2	26.8 ± 1.1
25–26	55 (38)	52 (35)
27–28	88 (62)	96 (65)
Birth weight, mean ± SD, g	894 ± 247	893 ± 241
Male sex	65 (45)	86 (58)
Birth weight <10th percentile for gestational age	31 (22)	32 (22)
Singleton birth	98 (69)	101 (68)

Unless otherwise indicated, data are n (%). pPROM, prolonged premature rupture of membranes.

Moreover, the overall rate of BPD was 35% (50 of 143) in the control group and 38.5% (57 of 148) in the SLI group; the rate of BPD in patients surviving at 36 weeks of postmenstrual age was 53.2% (50 of 94) in the control group and 54.8% (57 of 104) in the SLI group. The mortality before week 36 postmenstrual age was 12.8% (12 of 94) in the control group and 15.4% (16 of 104) in the SLI group.

No significant differences were found between the 2 groups in the other secondary outcomes. Pneumothorax occurred in 1% (n = 2) of infants in the control group compared with 6% (n = 9) of infants in the SLI group, with an unadjusted odds ratio of 4.57 (95% CI: 0.97–21.50; P = .06) (Table 4). The clinical characteristics of infants who developed pneumothorax are detailed in the Supplemental Appendix.

There was no statistically significant heterogeneity in the effects of the SLI maneuver on the primary end point according to any of the mother and infant characteristics tested in the subgroup analyses (Fig 2).

TABLE 2 Primary and Secondary Outcomes

Outcome	Control Group (n = 143)	SLI Group (n = 148)	Unadjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio (95% CI)[a]
Primary outcome, n (%)					
MV within the first 72 h of life	93 (65)	79 (53)	0.62 (0.38–0.99)	.04	0.57 (0.33–0.96)
Secondary outcomes, n (%)					
MV within the first 3 h of life	73 (51)	66 (45)	0.77 (0.49–1.22)	.27	0.72 (0.43–1.22)
BiPAP	47 (33)	63 (43)	1.51 (0.94–2.44)	.09	1.51 (0.93–2.43)
Nasal IMV	36 (25)	39 (26)	1.06 (0.63–1.80)	.85	1.07 (0.63–1.81)
Surfactant	110 (77)	109 (74)	0.84 (0.49–1.43)	.52	0.88 (0.50–1.56)
SIMV/SIPPV/PSV	90 (63)	86 (58)	0.82 (0.51–1.31)	.43	0.84 (0.51–1.39)
HFV	31 (22)	32 (22)	1.00 (0.57–1.74)	.99	1.03 (0.58–1.83)
Any mechanical ventilation	98 (69)	88 (59)	0.67 (0.42–1.10)	.11	0.68 (0.41–1.13)
BPD[b,c]	50 (35)	57 (39)	1.17 (0.80–1.71)[d]	.42	1.14 (0.78–1.69)[d]
Death[c]	12 (8)	17 (11)	1.37 (0.66–2.88)[d]	.40	1.39 (0.66–2.93)[d]

BiPAP, bilevel positive airway pressure; HFV, high-frequency ventilation; PSV, pressure support ventilation; SIMV, synchronized intermittent MV; SIPPV, synchronized intermittent positive pressure ventilation.

[a] Adjusted for center and gestational age.

[b] Defined by the use of supplemental oxygen at a postmenstrual age of 36 weeks.

[c] Proportions are estimates of cumulative incidence of events in the presence of competing risks.

[d] Unadjusted hazard ratio (95% confidence interval).

DISCUSSION

This multicenter, randomized controlled trial was conducted to determine if the use of SLI in the delivery room followed by early nCPAP would reduce the need for MV and improve respiratory outcome in preterm infants compared with the sole use of nCPAP. This strategy was found to be effective in decreasing the need for MV within the first 72 hours of life: during this period, 53% of infants were mechanically ventilated compared with 65% in the control group, with no significant adverse effects. These outcomes may be explained by the lung recruitment and FRC achievement provided by SLI, as well as the avoidance of lung collapse allowed by PEEP. This strategy might also improve the distribution of exogenous surfactant[20] and markedly increase pulmonary blood flow, thus leading to an improved speed of circulatory recovery.[21]

The SLI procedure combined with early nCPAP did not decrease the overall need for and duration of noninvasive respiratory support and MV, need for surfactant, or occurrence of BPD. Our results agree with the randomized controlled trials of Harling et al[22] and Lindner et al,[4] although both these studies lacked power because of small sample sizes. te Pas et al[5] found a decrease in the need for MV at 72 hours of life, but in their study, the SLI procedure also decreased the average duration of ventilatory support and the occurrence of moderate/severe BPD. These differences may have several explanations: the infants in the te Pas et al study received "rescue" SLI (if they had "no signs of spontaneous breathing or spontaneous breathing present, but signs of poor air entry"), whereas our infants had prophylactic treatment; they were also more mature than infants in our study (<33 vs <29 weeks of gestation) and fewer therefore had RDS (54% vs 94% in the control groups). The

TABLE 3 Other Secondary Outcomes

Outcome	Control Group (n = 143)	SLI Group (n = 148)	P
Highest F_{IO_2}, %	35 (30–50)	40 (25–45)	.57
Surfactant doses, h	1 (1–2)	1 (1–2)	.55
nCPAP duration, h	190 (47–500)	218 (42–480)	.88
BiPAP duration, h	138 (48–336)	132 (50–432)	.62
Nasal IMV duration, h	96 (23–234)	108 (24–320)	.63
SIMV/SIPPV/PSV duration, h	118 (24–216)	96 (24–288)	.81
HFV duration, h	72 (16–150)	94 (33–177)	.58
Duration of in-hospital stay, d[a]	75 (60–101)	83 (61–107)	.22

Data are presented as median (interquartile range). BiPAP, bilevel positive airway pressure; HFV, high-frequency ventilation; PSV, pressure support ventilation; SIMV, synchronized intermittent MV; SIPPV, synchronized intermittent positive pressure ventilation.

[a] Proportions are estimates of cumulative incidence of events in presence of competing risks.

infants enrolled in our study were thus at higher risk of developing BPD than the infants enrolled in the study of te Pas et al.

In the study by te Pas et al,[5] infants in the SLI group were assisted in the delivery room by using a T-piece ventilator that is capable of supplying a consistent PEEP, whereas infants in the control group were assisted with the use of a self-inflating bag and mask that supplies only minimal PEEP. In our study, the control group was treated in the delivery room with nCPAP by using a T-piece ventilator that provided a PEEP of 5 cm H_2O. Therefore, the decrease in BPD observed in the te Pas et al study group may be due to the early delivery of SLI plus PEEP rather than only to the delivery of SLI, and this effect may be enhanced by the lack of PEEP in the control group. It has been demonstrated in a rabbit model of RDS that ventilation without an SLI but with PEEP gradually recruits FRC, whereas ventilation without an SLI or PEEP does not permit the recruitment of FRC.[7] Thus, the nCPAP delivery to the control infants in the present study could have attenuated the BPD-preventing effect of SLI in our patients, allowing them a gradual recruitment of FRC despite the lack of SLI. These considerations seem to be confirmed by the similar occurrence of BPD in our study and that of the control group from the study of te Pas et al[5] (35% vs 34%). This finding indicates a similar risk of developing BPD even though the gestational age in the control subjects of te Pas et al is almost 3 weeks higher than ours, which may be explained by the lack of PEEP delivery in the delivery room.

Conversely, the pivotal role of ventilator-induced lung injury in the pathogenesis of BPD[1] could have overwhelmed the beneficial effect of SLI. In fact, it is remarkable that the majority of our patients (control group: 68%; SLI group: 59%) received MV, and it is reasonable that any beneficial effect of a single procedure performed in the first minutes of life, reducing the need for MV in the first 3 days of life, may be negated by the following MV. This suggestion is in agreement with the findings of Hilman et al,[23] who demonstrated in preterm lambs that the proinflammatory lung responses to SLI followed by MV were significantly higher than the responses to SLI alone. It is well known, however, that the pathogenesis of BPD includes several additional factors, such as hyperoxia, infection, and undernutrition, and no single "magic bullet" can prevent it.[24]

TABLE 4 Comparison of Other Collected Data

Outcome	Control Group (n = 143)	SLI Group (n = 148)	Unadjusted Odds Ratio (95% CI)	P
RDS	134 (94)	133 (90)	0.60 (0.25–1.41)	.23
Pneumothorax	2 (1)	9 (6)	4.57 (0.97–21.50)	.06
Interstitial emphysema	2 (1)	7 (5)	3.50 (0.72–17.10)	.09
Pharmacologic treatment of PDA	70 (49)	88 (59)	1.53 (0.96–2.43)	.07
Surgical closure of PDA	8 (6)	5 (3)	0.59 (0.19–1.85)	.36
IVH	28 (20)	37 (25)	1.37 (0.79–2.39)	.27
Grade ≥3	8 (6)	12 (8)	1.49 (0.59–3.76)	.39
PVL	5 (4)	1 (1)	0.19 (0.02–1.63)	.08
NEC	4 (3)	7 (5)	1.73 (0.49–6.03)	.38
ROP[a]	58 (41)	60 (41)	0.99 (0.63–1.60)	.99
Grade ≥3	12 (8)	14 (9)	1.14 (0.51–2.56)	.75
Sepsis	44 (31)	54 (36)	1.29 (0.79–2.11)	.30

Data are presented as n (%). IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

[a] Proportions are estimates of cumulative incidence of events in the presence of competing risks.

In the present study, the frequency of pneumothorax (6% vs 1%) and interstitial emphysema (5% vs 1%) was higher in the SLI group than in the control group. Previous studies found no evidence of an increased rate of pneumothorax in SLI-treated infants and did not report data on the occurrence of interstitial emphysema.[4,5,22] Although the difference was not statistically significant, we believe that this finding deserves consideration because it might suggest that our SLI maneuvers (25 cm H_2O for 15 seconds) might be too aggressive. The results of the study by Hilman et al[23] are reassuring with regard to the duration of our procedure, but it is possible that the pressure used is excessive in extremely preterm infants. This possibility may be more probable when the SLI procedure is applied as prophylaxis, as in our study, involving infants with or without mild RDS whose lung compliance at birth is better than that of infants with moderate or severe RDS and at higher risk of hyperinflation damage. Nonetheless, it must be noted that the median age of SLI infants developing

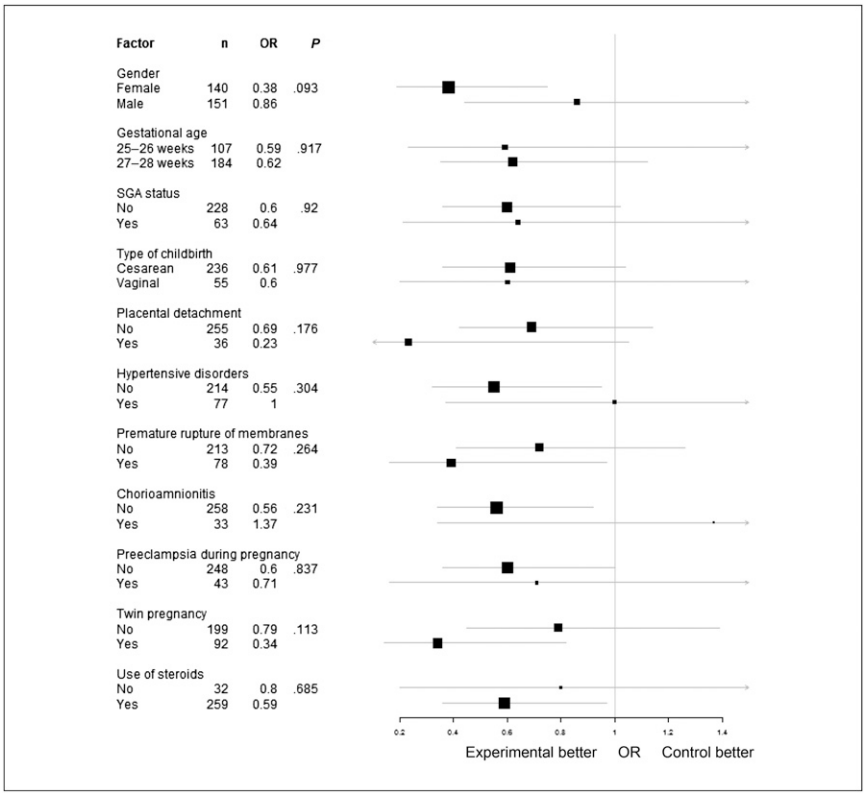

FIGURE 2

Effect of the SLI maneuver in the delivery room versus standard assistance on the occurrence of MV within the first 72 hours of life according to subgroup. OR, odds ratio; SGA, small for gestational age.

pneumothorax was 70 hours, ~3 days after SLI was performed.

The limitations of our study are that it was not blinded, the staff performing the study also cared for the infants later on, and that it was a multicenter study, which may have allowed differences in the clinical management of infants that affected their outcome. We tried to minimize these biases by maintaining strict criteria and definitions during the trial. Moreover, there was a significant discrepancy between predicted rate of intubation within the first 72 hours of life (35% in control subjects and 20% in the SLI group) and actual rates observed in the study. We speculate that this outcome occurred because our population was at higher risk for MV than that enrolled in the reference study,[18] which excluded infants with severe birth asphyxia, endotracheal intubation for resuscitation, or insufficient respiratory drive and randomized to treatment only infants in stable clinical condition. However, the difference in MV between the SLI and control groups was, as expected, ~15%.

CONCLUSIONS

Our study found that SLI followed by early CPAP in the delivery room decreased the need for MV in the first 72 hours of life in extremely preterm infants compared with nCPAP alone but did not decrease the need for respiratory support and the occurrence of BPD. We believe that other clinical studies are necessary to investigate the effectiveness of SLI in improving outcomes in extremely preterm infants. Until these studies are available, the SLI maneuver cannot be recommend as routine prophylactic assistance in preterm infants in the delivery room.

Drs Dani and Lista conceptualized and designed the study and wrote the manuscript; Drs Agosti, Biban, Bellettato, Boldrini, Del Vecchio, Gazzolo, Gizzi, Magaldi, Messner, Mosca, Sandri, Scopesi, Trevisanuto, and Vento made substantial contributions to the conception and design of the study protocol and critically revised the protocol; and Dr Boni provided substantial contributions to the conception and design of the study protocol, prepared electronic data sheets, was responsible for the web-based electronic case record form, performed the statistical analyses, and critically revised the study. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01440868).

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