

Lung Recruitment Improves the Efficacy of Intubation-Surfactant-Extubation Treatment for Respiratory Distress Syndrome in Preterm Neonates, A Randomized Controlled Trial

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Abstract

Background: Lung recruitment is a maneuver in preterm neonates at birth, which may decrease the length of intubation. This study aimed to compare the therapeutic efficacy of lung recruitment plus intubation-surfactant-extubation (INSURE) procedure and INSURE alone for the preterm neonates with respiratory distress syndrome.

Methods: A total of 184 preterm neonates with respiratory distress syndrome from 2017 to 2019 were enrolled and randomized into the lung recruitment group receiving lung recruitment (25 cm H₂O for 15 seconds) plus INSURE and the control group receiving INSURE only. The primary outcome was the need for mechanical ventilation (MV) within 72 h after extubation. The secondary outcomes include the duration of intubation, noninvasive ventilation, total oxygen therapy, hospitalization, and other complications.

Results: Compared to the control group, the lung recruitment group had a significantly lower proportion of preterm neonates need for MV within 72 h after extubation (23% vs. 38%, P=0.025) and pulmonary surfactant administration, as well as shorter the MV duration. Multivariate logistic regression analysis demonstrated that the control group had a 2.17-time higher risk for need for MV than the lung recruitment group (OR: 2.17, 95% CI: 1.13-4.18; P=0.021). In the mothers with hypertension, the infants presented a 2.41-time higher risk for requiring MV as compared with those of mothers with normotension (OR: 2.41, 95% CI: 1.15-5.05; P=0.020).

Conclusion: These data suggested that lung recruitment plus INSURE can reduce the need for MV within 72 hours after extubation without increasing the incidence of complications and mortality.

Background

Neonatal respiratory distress syndrome (RDS) is a leading cause of morbidity in preterm neonates caused by pulmonary surfactant insufficiency and pulmonary structural immaturity[1]. The purpose of the management of RDS is to provide interventions that not only maximize survival but also minimize potential adverse effects. According to the European Consensus Guidelines for the Management of RDS, preterm infants should be stabilized with the Continuous Positive Airway Pressure (CPAP) of at least 6 cm H₂O via mask or nasal prongs in spontaneously breathing[2]. Gentle positive pressure lung inflation using about 20–25 cm H₂O peak inspiratory pressure should be used for persistently apneic or bradycardic infants[2]. The European Consensus Guideline also suggests that for infants failure in CPAP treatment, the INSURE strategy should be considered[3]. The INSURE technique consists of an INTubation-SURfactant-Extubation procedure, which has been shown to reduce the need for mandatory ventilation (MV), the duration of respiratory support, and the need for surfactant replacement in preterm infants with RDS [4].

Lung recruitment is used for preterm infants with respiratory failure and RDS to ensure early and effective creation of FRC to prevent lung damage [5, 6]. Lung recruitment is a maneuver using the peak pressure of

25–30cmH₂O for 10–20 s[7]. Previous animal studies have shown that lung inflation can provide more stable tidal volume and uniform lung ventilation with improved functional residual capacity (FRC) as compared with intermittent ventilation[8, 9]. Clinical trials also demonstrate that the application of lung recruitment at birth in preterm infants with respiratory distress decreases the need for MV[9–12]. Nevertheless, contradicting these findings, some trials reported lung inflation has no superior effect [13, 14]. A Systematic Review and Meta-analysis showed that 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[15]. A review by Bruschetti et al. have suggested that there was insufficient evidence that lung inflation is superior to IPPV in terms of MV requirement and other important respiratory outcomes[15]. On the other hand, lung recruitment has not attracted people's attention and applied in clinical practice in China.

To further evaluate the therapeutic efficacy and safety of lung recruitment, therefore, this study aimed to investigate if lung recruitment is capable of improving the efficacy of INSURE treatment for respiratory distress syndrome in preterm neonates. We conducted a prospective study to compare the therapeutic efficacy of lung recruitment plus INSURE and INSURE alone for the preterm neonates with respiratory distress syndrome.

Methods

Participants and study design

This was a prospective randomized controlled trial. A total of 184 preterm neonates with respiratory distress syndrome in the department of Neonatology in maternal and child health hospital in DongGuan during 2017 to 2019 were enrolled and randomized into the lung recruitment group and the control group. This trial was registered at the Chinese Clinical Trial Registry (ChiCTR1800020125). The trial flow diagram was shown in Fig. 1.

Inclusion criteria were: 1) the infants with gestational age from 24 to 32 weeks; 2) birth weight less than or equal to 1800 g; 3) definite diagnosis of RDS by clinical syndrome and X-ray findings; 4) all infants would receive continuous CPAP within 24 hours after the parent's consent. The infants with severe congenital malformation or required endotracheal intubation in the delivery room were excluded. This study was approved by the institutional review board of our hospital. Written informed consent was obtained from the patient. Our study adheres to CONSORT guidelines.

Sample size calculation

We hypothesized that lung recruitment with INSURE could reduce the probability of mechanical ventilation after conventional INSURE therapy from 50% to 30%. The sample size was increased to 184 cases to give 80% power ($\alpha=0.05$).

Randomization and treatment

The sequence numbers were kept in opaque sealed envelopes that were opened just before infants meet the inclusion criteria but not the exclusion criteria by a person not involving in the management of the infants. The lung recruitment group received Lung recruitment 15s by a T-piece resuscitator after endotracheal intubation for pulmonary surfactant 200mg/Kg into the trachea and then the catheter was removed, followed by continuous positive airway pressure. The control group only received endotracheal intubation without sustained lung inflation. The other processes were the same as the intervention group.

Outcome measures

The incidence of reintubation within 72 hours was recorded. The reintubation was defined as follows: 1) infants failure in NCPAP treatment after INSURE therapy; 2) the oxygen saturation $<90\%$ with a $FiO_2 \geq 0.40$ under NCPAP. The following data were recorded: durations of intubation, noninvasive ventilation, total oxygen therapy, and hospitalization and the complications, including pneumothorax, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy (ROP), patent ductus arteriosus (PDA), persistent pulmonary hypertension (PPHN), bronchopulmonary dysplasia (BPD) and death. The IVH was defined as a spectrum of hemorrhage brain injury most typically occurring in the first week of life in very preterm babies according to the NIH Consensus Development Conference [16]. BPD was defined according to the oxygen requirement as follows: Mild BPD- a need for supplemental oxygen (O_2) for ≥ 28 days but not at 36 weeks' postmenstrual age (PMA) or discharge; moderate BPD- a need for supplemental O_2 for 28 days plus treatment with $<30\%$ O_2 at 36 weeks' PMA; severe BPD- a need for supplemental O_2 for ≥ 28 days plus $\geq 30\%$ O_2 and/or positive pressure at 36 weeks' PMA [17]. Meanwhile, we have collected blood gas analysis results were collected before extubation, at 1, 6, 12, 24, 48, and 72 hours after extubation.

Statistical analysis

Statistical data were analyzed by using Student's t-test for parametric and the Mann–Whitney U test for non-parametric continuous variables; and χ^2 test or Fisher's exact test (if any expected value <5 was found) for categorical variables. Repeated measurement data were using repeated measures in the General Linear Model. Univariate and multivariate logistic regression were used to investigate the association of independent variables associated need for MV within 72 hours after extubation. The variables which were significant in univariate results would be entered into a multivariate model, and the variables which were significant in multivariate results would be considered as associated factor with the primary outcome. The statistical significance level for all the tests was set at a P-value < 0.05 . All analyses were performed using IBM SPSS Version 20 (SPSS Statistics V20, IBM Corporation, Somers, New York).

Results

Patients' demographic and clinical characteristics

A total of 184 preterm neonates with respiratory distress syndrome from 2017 to 2019 were enrolled and divided into the lung recruitment group which received lung recruitment plus INSURE and the control group which received INSURE only (n = 92 for each group). Patients' demographic and clinical characteristics were summarized in Table 1. Both the lung recruitment group and the control group had a mean gestational age around 29.7 weeks and a mean birth weight around 1.30 kg. There was no significant difference in infants at birth including gestational age, birth weight, gender, and rate of cesarean section (all P > 0.05). Meanwhile, the mother's characteristics were also comparable between the two groups except that the control group had a higher incidence of gestational diabetes mellitus than the control group (P = 0.005).

Table 1
Patients' demographic and clinical characteristics

	lung recruitment group (n = 92)	Control group (n = 92)	t/χ ²	P
Gestational age, mean(SD),wk	29.75 ± 1.86	29.69 ± 1.66	0.218	0.828
Birth weight,mean(SD),kg	1.32 ± 0.28	1.29 ± 0.25	0.719	0.473
Gender,boy,n(%)	55(60)	60(65)	0.580	0.446
Cesarean section,n(%)	56(61)	65(71)	1.955	0.162
Mother, n(%)	54(59)	48(52)	0.792	0.374
Antenatal steroids				
gestational diabetes mellitus	8(9)	22(24)	7.806	0.005
amniotic fluid pollution	7(8)	10(11)	0.583	0.445
intrauterine infection	29(32)	34(37)	0.603	0.437
Hypertension disorders	21(23)	19(21)	0.128	0.721
premature rupture of membranes	16(17)	20(22)	0.553	0.457
Asphyxia, n(%)	18(20)	15(16)	0.332	0.564
Apgar,1 min,mean(SD)	8.51 ± 1.81	8.71 ± 1.96	0.703	0.483
Apgar,5 min,mean(SD)	9.42 ± 0.70	9.49 ± 0.87	0.560	0.576
Apgar,10 min,mean(SD)	9.51 ± 1.12	9.59 ± 0.65	0.562	0.575

Therapeutic Outcomes And Complications

Therapeutic outcomes were compared between the two groups. As shown in Table 2, the lung recruitment group had significantly fewer preterm neonates need for MV within 72 h after extubation as compared with the control group (23% vs. 38%, $P = 0.025$). In addition, the MV duration and the frequency of pulmonary surfactant administration and highest FiO_2 of lung recruitment group were significantly less in the lung recruitment group than in the control group (both $P < 0.05$, Table 2). Nevertheless, no other secondary outcomes were significantly different between the two groups (all $P > 0.05$, Table 2).

Table 2
The comparison of therapeutic outcomes between the two groups

	lung recruitment group (n = 92)	Control group (n = 92)	Z/ χ^2	P
Primary outcome				
MV within 72 h after extubation	21(23)	35(38)	5.031	0.025
Second outcomes				
Mechanical ventilation duration, *,d	0(0-3.8)	1.5(0-9)	2.73	0.006
Noninvasive ventilation duration, *,d	11.6(6-28)	13.8(7-25.4)	0.426	0.670
Total oxygen therapy duration, *,d	22.6(9.7-35)	26.5(14-39)	0.804	0.421
Hospitalization, *,d	45(32-62)	47(38-67)	0.869	0.385
Pulmonary surfactant operate duration, *,h	3(1.5-5)	3(2-6)	1.072	0.284
Pulmonary surfactant frequency, *	1.05 ± 0.23	1.17 ± 0.44	2.199	0.028
Highest FiO_2 , *	0.32 ± 0.05	0.35 ± 0.09	0.869	0.004
*:median (P25,P75)				

The 4 parameters of blood gas were compared between the two groups, including PH value (Fig. 2A), PCO_2 (Fig. 2B), PO_2 (Fig. 2C), and Base Excess (BE, Fig. 2D). No significant difference was observed between the two groups ($P > 0.05$).

The complications were compared between the two groups. As shown in Table 3, there was no significant difference in the incidences of complications between the two groups (all $P > 0.05$). Two cases and 4 cases died after the treatment due to abandoning treatment in the lung recruitment group and the control group, respectively.

Table 3
The comparison of complications between the two groups.

	lung recruitment group (n = 92)	Control group (n = 92)	χ^2	P
BPD, n(%)	30(33)	37(40)	1.15	0.284
mild BPD	17(57)	28(76)	2.714	0.099
moderate-severe BPD	13(43)	9(24)		
IVH, n(%)	8(9)	17(19)	3.749	0.053
pneumothorax, n(%)	2(3)	3(3)	0.000	1.000
NEC, n(%)	10(11)	15(16)	1.157	0.282
PDA, n(%)	21(23)	24(26)	0.265	0.607
ROP, n(%)	19(21)	14(15)	0.923	0.337
PPHN, n(%)	2(2)	4(4)	0.689	0.406
Death, n(%)	2(2)	4(4)	0.689	0.406
BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, symptomatic patent ductus arteriosus; ROP, retinopathy of prematurity; PPHN,				

Independent factors associated with the need for MV within 72 hours after extubation

To further investigate the risk factor of requiring MV within 72 hours after extubation, univariate, and multivariate logistic regression models were performed. As shown in Table 4, only two factors were identified as independent risk factors in the multivariate analysis. The results indicated that the control group had a 2.17-time higher risk for need for MV than the lung recruitment group (OR: 2.17, 95% CI: 1.13–4.18; P = 0.021). In the mothers with hypertension, the infants presented a 2.41-time higher risk for requiring MV as compared with those of mothers with normotension (OR: 2.41, 95% CI: 1.15–5.05; P = 0.020).

Table 4
The parameter of blood gas comparison between two groups

Parameters	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Group				
lung recruitment	ref.	-	ref.	-
Control	2.08 (1.09 to 3.95)	0.026	2.17 (1.13 to 4.18)	0.021
Gestational age, week	0.84 (0.70 to 1.00)	0.055		
Birth weight, kg	0.51 (0.16 to 1.66)	0.263		
Gender of newborn				
Male	ref.	-		
Female	0.72 (0.37 to 1.39)	0.322		
Delivery method				
NSD	ref.	-		
CS	1.14 (0.59 to 2.23)	0.692		
Mother				
Antenatal steroids, yes	0.59 (0.31 to 1.12)	0.105		
Gestational diabetes mellitus, yes	0.98 (0.42 to 2.29)	0.955		
Amniotic fluid pollution, yes	0.95 (0.32 to 2.83)	0.923		
Intrauterine infection, yes	1.53 (0.80 to 2.94)	0.198		
Hypertension, yes	2.28 (1.11 to 4.71)	0.026	2.41 (1.15 to 5.05)	0.020
Premature rupture of membranes, yes	0.85 (0.38 to 1.91)	0.699		
Asphyxia				

NSD, normal spontaneous delivery; CS, cesarean section.

	Univariate	Multivariate
No	ref.	-
Yes	1.91 (0.88 to 4.16)	0.102
Apgar – 1 min	0.87 (0.74 to 1.02)	0.076
Apgar – 5 min	0.80 (0.55 to 1.18)	0.261
Apgar – 10 min	0.61 (0.36 to 1.03)	0.066
NSD, normal spontaneous delivery; CS, cesarean section.		

Discussion

In this study, we compared the therapeutic efficacy of lung recruitment plus INSURE and INSURE alone for the preterm neonates with respiratory distress syndrome. The results showed that compared to the control group, the lung recruitment group had a significantly lower proportion of preterm neonates' need for MV within the 72 h after extubation (23% vs. 38%, $P = 0.025$) and pulmonary surfactant administration, as well as shorter the MV duration. Nevertheless, there were no significant differences in other secondary outcomes, 4 parameters of blood gas, and the incidence of complications between the two groups. Multivariate logistic regression analysis demonstrated that the control group had a 2.17-time higher risk for need for MV than the lung recruitment group (OR: 2.17, 95% CI: 1.13–4.18; $P = 0.021$). In the mothers with hypertension, the infants presented a 2.41-time higher risk for requiring MV as compared with those of mothers with normotension (OR: 2.41, 95% CI: 1.15–5.05; $P = 0.020$). Taken together, these data suggested that lung recruitment plus INSURE can reduce the need for MV within 72 hours after extubation without increasing the incidence of complications and mortality.

Listae et al. conducted a clinical trial of preterm infants with respiratory distress treated with sustained lung inflation (25 cm H₂O, sustained for 15 s) at birth and concluded that the application of sustained lung inflation at birth in preterm infants with respiratory distress may decrease the need for MV without inducing evident adverse effects as compared with a historical control group [18]. Consistent with this observation, our results suggested that lung recruitment can effectively reduce the need for MV without increase the adverse effects. In addition, the MV duration and pulmonary surfactant frequency were both reduced in the lung recruitment group as compared with the control group, which were in line with previous findings [11, 12, 18–20]. The lung recruitment technique might positively affect the clearance of lung fluid and allows a more even distribution of air throughout the lungs, thus facilitating the formation of FRC [21]. Therefore, the beneficial effects may be attributed to lung recruitment and FRC achievement provided by lung recruitment and the alveolar expansion by inflation.

BPD is a major complication of preterm birth [22] and has a complicated pathogenic mechanism. Immature lung development, acute lung injury, and abnormal repairment after injury are key points leading to BPD[23]. One of the most important factors in the pathogenesis of BPD is Ventilator-induced lung injury[24]. In this study, the incidence of BPD was lower in the lung recruitment group than the control group(33% VS 40%), but the difference did not reach statistical significance. The incidences of different severe BPDs also showed no statistical difference between the two groups. This result suggested that lung recruitment did not increase the accidence of BPD. In this study, lung recruitment did not increase the incidences of adverse effects, including IVH, NEC, PDA, ROP, which is in agreement with previous studies[13, 14, 18, 25].

In this study, two cases had pneumothorax in the lung recruitment group and three cases had pneumothorax in the control group, suggesting that lung recruitment did not increase the risk of pneumothorax. This result is consistent with previous reports[10, 14, 15, 25]. By contrast, Lista et al. have reported that patients with lung inflation treatment have a 4.57 times-high risk of pneumothorax than the control patients [11]. The discrepancy might be attributed to different study subjects, and the effect of lung recruitment on pneumothorax should be further investigated.

In this study, no difference in mortality was found between the two groups. Two cases of death in the lung recruitment group were due to the abandonment of parents but not pneumothorax or other severe complications. This result suggested lung recruitment did not increase mortality. The comparison in the blood gas parameters between the two groups showed no significant difference, suggesting that lung recruitment did not impact the circulation and the rate of acidosis. This may be due to the comprehensive influence of ventilation improvement.

There are still some limitations to this study. First, the study was not double-blinded. The staffs performing the study also cared for the infants later on, which might affect the outcome. We tried to minimize this bias by strictly follow the trial protocol during the whole trial. In addition, this was a single-center trial and the sample size was still relatively small. In the future, a large multicenter trial should be conducted to validate the findings of this study.

Conclusion

Our study found that lung recruitment plus INSURE can effectively reduce the need for MV within 72 hours after extubation without increasing the incidence of complications and mortality.

Abbreviations

RDS: respiratory distress syndrome; CPAP: Continuous Positive Airway Pressure; MV: mandatory ventilation; SLI: Sustained Lung Inflation; FRC: functional residual capacity; IVH: intraventricular hemorrhage; NEC: enterocolitis; ROP: retinopathy; PDA: patent ductus arteriosus; PPHN: persistent pulmonary hypertension; BPD: bronchopulmonary dysplasia; PMA: postmenstrual age

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Maternal and Child Health Hospital in Dongguan [2016(21)]. Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for the publication.

Availability of data and materials

All the data and materials have been presented in the main paper.

Competing interests

None declared.

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Authors' contributions

We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. Dr. YY designed the study and wrote the protocol, Drs. YW, RM and ZL acquired and collected the data, Dr. SJ and DH interpret the data and undertook the statistical analysis, Dr. LM wrote the first draft of the manuscript and mainly revised the manuscript. All authors approved the final version of this manuscript.

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Figures

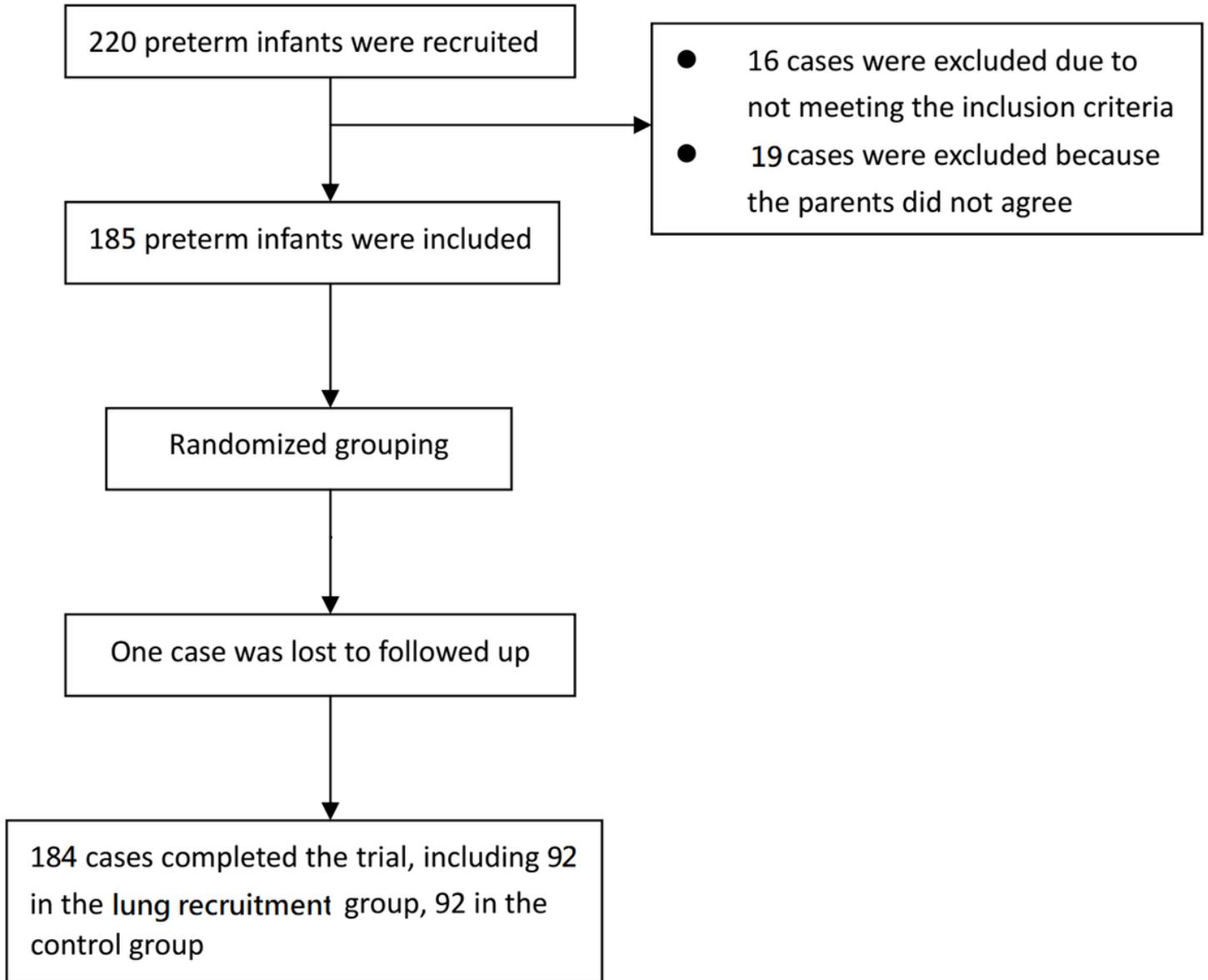


Figure 1

The trial flow diagram of this study.

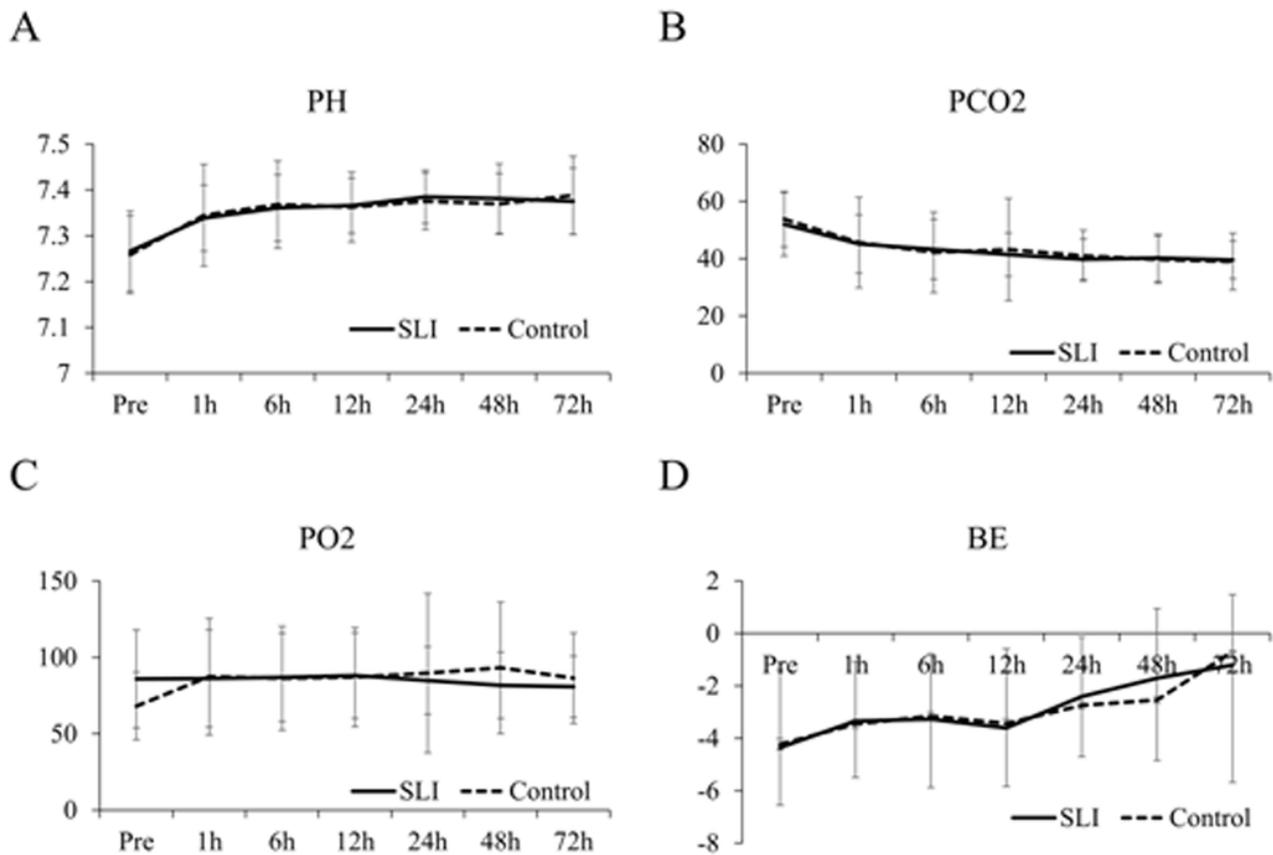


Figure 2

The change of PH (A), PCO₂ (B), PO₂ (C), and BE (D) before extubation (pre) to 72 hours after extubation.

Supplementary Files

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