

# Sustained Lung Inflation in Preterm Infants with Signs of Respiratory Distress: A Randomized Controlled Trial

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## Abstract

**Background:** The role of sustained lung inflation (SI) in neonatal resuscitation at birth as a substitute for, or an adjuvant to positive pressure ventilation (PPV) has been previously examined. This study was conducted to examine the effect of applying SI in preterm infants, who did not need PPV at birth but showed signs of respiratory distress within the first minutes of life, on their mortality and some common morbidities.

**Materials and Methods:** In this double-blind randomized clinical trial, seventy-four preterm infants with gestational age 28–33 6/7 weeks and birth weight more than 1000 g in whom signs of respiratory distress appeared within five to ten minutes after birth were randomly assigned to receive nCPAP alone (nCPAP-only group) or a 10-second sustained inflation with 20 cmH<sub>2</sub>O pressure followed by nCPAP (SI group).

**Results:** The need for surfactant administration was significantly less ( $P = 0.003$ ) and the length of hospital stay was significantly shorter in the SI group ( $P = 0.005$ ), but the duration of nCPAP was significantly longer in this group ( $P = 0.003$ ). There was no statistically significant difference between the two groups in terms of the need for and duration of mechanical ventilation and also, other secondary outcomes.

**Conclusions:** Applying SI within the first minutes after birth in preterm infants with early signs of respiratory distress can reduce the need for exogenous surfactant and the length of hospital stay. Further studies on the role of this modality in the management of RDS in neonates, especially its effect on long-term cardiopulmonary and neurodevelopment outcomes, are recommended.

**Keywords:** Infant, inflation, lung, premature, respiratory distress syndrome

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## INTRODUCTION

Taking the first breaths at birth is crucial for the recruitment of the fluid-filled lungs of neonates and the establishment of functional residual capacity (FRC) by replacing the fluid with air in the terminal bronchioles and alveoli.<sup>[1]</sup> Most of term infants can effectively do this; in contrast, the majority of preterm infants, especially the thinner ones, may have difficulties in this way for some reasons including their lung immaturity, surfactant deficiency, weak respiratory muscles, and high chest wall compliance.<sup>[2,3]</sup> The role of nCPAP, beginning as soon as indicated after birth, in achieving proper FRC, especially in preterm infants, had been already well known.<sup>[4]</sup> In recent years, the use of sustained lung

inflation (SI)—an inflation pressure with longer duration than those of conventional positive pressure ventilation (more than 1–5 s)—in preterm infants, mainly during their resuscitation at birth, has been studied.<sup>[5]</sup> The SI is supposed to help the preterm neonates to achieve a more uniformly distributed aeration of the respiratory units and to establish the FRC while enhancing the reabsorption of lung fluids.<sup>[6,7]</sup> In some studies, its effect on the need for endotracheal intubation and mechanical ventilation, development of chronic lung disease (CLD), mortality, and some other morbidities have been examined and different results reported. Systematic reviews and meta-analyses of these studies have shown that most of the results were controversial and might be inconsistent.<sup>[8–12]</sup> In many of these studies, SI has

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been applied at birth in the delivery room as a substitute for, or an adjuvant to positive pressure ventilation. Recently, some studies have assessed the effect of this type of lung recruitment maneuver on adult patients with acute respiratory distress syndrome (ARDS).<sup>[13]</sup> In the present study, we examined the effect of applying SI within the first minutes after birth in spontaneously breathing preterm infants with early signs of respiratory distress, on their mortality and some common morbidities.

## MATERIALS AND METHODS

From January 2020 to January 2021, we conducted this double-blind randomized clinical trial in two neonatal intensive care units (NICUs) in two teaching tertiary hospitals affiliated with our university. The study protocol was approved by the ethics committee of the university; the registration number was IR.MUI.MED.REC.1398.449. Inborn infants with gestational age 28–33<sup>6/7</sup> weeks and birth weight more than 1000 g in whom signs of respiratory distress appeared within five to ten minutes after birth were included. Infants who needed positive pressure ventilation for stabilization at birth (apnea, gasping, or heart rate < 100 bpm) and those with a history of maternal chorioamnionitis or life-threatening congenital anomalies were excluded from the study. Based on data extracted from the mentioned previous studies,<sup>[14]</sup> if  $d$  was considered equal to 0.2, thirty-seven infants were needed for this study to achieve 80% power and  $\alpha$  of 0.05. Informed consent was obtained from the parents before the delivery.

### Interventions

Immediately after birth, all infants were put under a radiant warmer and regarding the neonatal resuscitation program (published by the American Academy of Pediatrics and American Heart Association) received the initial steps of newborn care, if needed. Those who stabilized after these initial steps were observed in the delivery room for a while before transporting to the NICU. Using computer-generated block randomization, infants in whom signs of respiratory distress appeared within the first five to ten minutes after birth were allocated to one of the two groups to receive nCPAP alone (nCPAP-only group) or sustained inflation followed by nCPAP (SI group). Infants in the SI group received 10-second sustained inflation with 20 cmH<sub>2</sub>O pressure by a T-piece resuscitator (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand) via binasal prongs (Argyle CPAP Nasal Cannulas, Covidien, Medline Industries, Mexico). After that, nasal CPAP (nCPAP) was immediately provided with 5 cmH<sub>2</sub>O pressure. For infants in the nCPAP-only group, respiratory support was provided only by nCPAP with the same setting and tools.

In both groups, gas flow was set at 10 L/min and oxygen concentration was primarily set at 21% to 30% and further adjusted in accordance with target oxygen saturation values, using a pulse oximeter with the sensor placed on the right hand or wrist. The neonates then were transported to the

NICU while receiving nCPAP with 5 cmH<sub>2</sub>O pressure. In the NICU, decisions about weaning the infants from nCPAP or increasing the pressure and FIO<sub>2</sub> and vice versa, surfactant administration, and mechanical ventilation were made using standard protocols.

The infants were followed until 36 weeks postmenstrual age or the 28<sup>th</sup> day of birth (whichever came later). To detect intraventricular hemorrhage (IVH), cranial ultrasound was performed on days 3, 7, and 14 of birth. A physician who made decisions about the management of these infants in the NICU and followed them during the entire period of the study was not aware of their group assignment.

### Outcome measurements

Demographic data included infants' gestational age and birth body weight, gender, and administration of antenatal glucocorticoids to the mother. Primary outcomes were the need for and duration of mechanical ventilation within the first 72 hours of birth, duration of nCPAP in the NICU, and need for administration of surfactant. Secondary outcomes included duration of need to supplemental oxygen, incidence of CLD (defined as oxygen requirement by the later of 36 weeks postmenstrual age or 28 days after birth), intraventricular hemorrhage (IVH) (grade II or more), necrotizing enterocolitis (NEC), pneumothorax, pulmonary hemorrhage, rate of mortality and length of hospital stay.

### Statistical analysis

Data were analyzed using SPSS software for Windows version 25 (SPSS Inc., Chicago, IL, USA). Independent *t* test and Mann–Whitney test were used to compare parametric and nonparametric continuous variables. A Chi-square test was applied for qualitative variables. *P* value < 0.05 was considered to be statistically significant.

## RESULTS

Ninety infants were assessed for eligibility. Parents of five infants refused participation of their child in the study and eleven infants lost to meet all inclusion criteria [Figure 1]. A total of 74 newborn infants were allocated to one of the two groups and completed the study. Baseline characteristics of participants are described in Table 1. There were no significant differences between groups (*P* > 0.05).

As shown in Table 2, the duration of need to nCPAP in the SI group was significantly longer than in nCPAP-only group (81.84 ± 76.43 h vs. 40.46 ± 25.01 h in SI and nCPAP-only groups, respectively; *P* = 0.003). The need for surfactant administration in the SI group was significantly less than nCPAP-only group (7 [18.9%] vs. 20 [54.1%] in SI and nCPAP-only groups, respectively; *P* = 0.003). The length of hospital stay in the SI group was also significantly less than nCPAP-only group (37.05 ± 10.18 d vs. 45.35 ± 14.24 d in SI and nCPAP-only groups, respectively; *P* = 0.005). There was no statistically significant difference between the two groups in terms of the need for and duration of mechanical

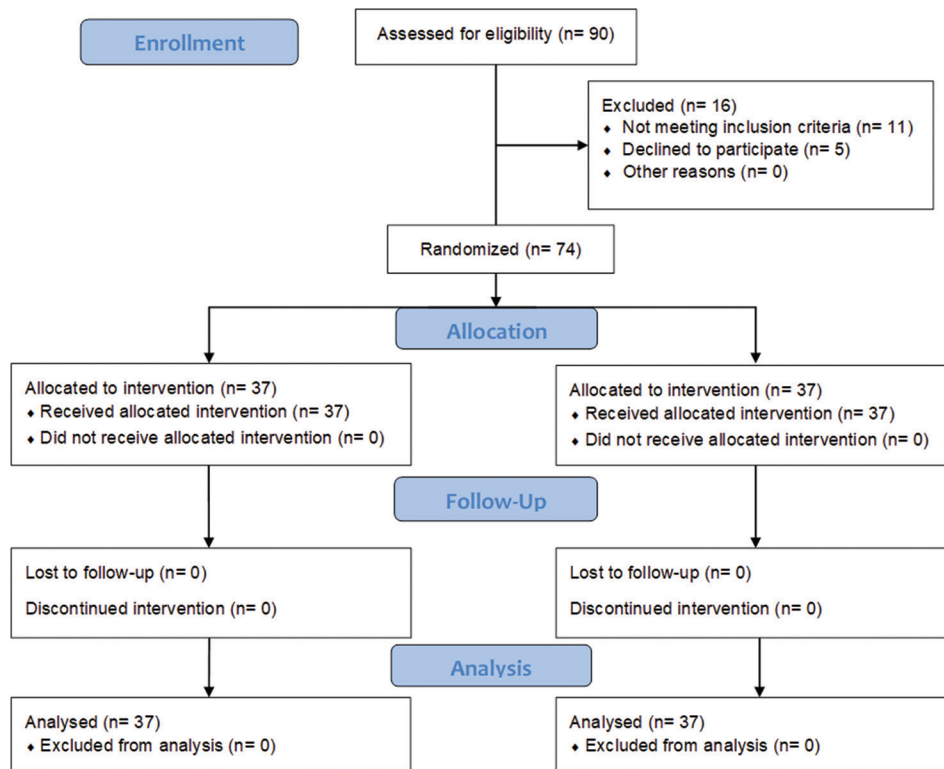


**Figure 1:** Patients' flow diagram (CONSORT)

**Table 1: Demographic and baseline characteristics of the preterm infants (n=37, for each study group)**

| Variable                                       | SI group       | nCPAP-only group | P     |
|------------------------------------------------|----------------|------------------|-------|
| Sex                                            |                |                  |       |
| Male                                           | 15 (40.5%)     | 20 (54.1%)       | 0.352 |
| Female                                         | 22 (59.5%)     | 17 (45.9%)       |       |
| Gestational age (weeks)                        | 31.21±2.08     | 31.95±1.38       | 0.079 |
| Birth body weight (g)                          | 1542.03±293.76 | 1598.92±337.93   | 0.442 |
| Mother received corticosteroid before delivery | 34 (91.9%)     | 33 (89.2%)       | 0.691 |

Data are presented as mean±SD or number (%), where applicable. SI group: received sustained lung inflation followed by nasal continuous positive airway pressure, nCPAP-only group: received nasal continuous positive airway pressure alone, SD=Standard deviation

ventilation (within the first 72 hours of birth), duration of oxygen requirement, and incidence of CLD, IVH (grade II or more), NEC, pneumothorax, pulmonary hemorrhage, and death ( $P > 0.05$ ).

## Discussion

The findings of our study showed that applying SI within the first minutes after birth in preterm infants with early signs of respiratory distress reduced the need for exogenous surfactant and the length of hospital stay; the time on nCPAP, however, was increased. As mentioned above, many of the previous trials in this field examined the role of SI in the resuscitation

of neonates at birth, especially premature infants, who did not respond to the initial steps of newborn care. In this study, we included preterm infants who only required these initial steps and did not need PPV for resuscitation but showed the first signs of respiratory distress.

In the study of Abuel Hamd *et al.*, they used SI followed by nCPAP in one group of preterm infants with a gestational age of 27–32 weeks and compared it with another group who received nCPAP alone. Similar to our study, there was no difference between groups in terms of the primary outcome of the study—need for intubation and mechanical ventilation within the first 72 hours of life—and also, mortality and CLD among survivors. In both groups, however, two subgroups of infants were defined based on the presence or absence of heart rate less than 100 bpm/min, gasping, apnea, labored breathing, or persistent cyanosis. These signs are considered as clinical eligibility criteria (CEC), indicating the need to PPV or CPAP. Infants with CEC in the SI group received SI as rescue; otherwise, they received that as prophylaxis. In the control group, infants with CEC received PPV if indicated; otherwise, CPAP was applied as rescue or prophylaxis. Rescue SI significantly reduced the primary outcome and mortality in infants with CEC. The primary outcome was also significantly reduced in infants with gestational age of less than 30 weeks who received prophylactic SI.<sup>[15]</sup> Infants with CEC in this study were more likely to have respiratory distress syndrome, as infants in our study. However, in contrast to our study, there were infants who had apnea, gasping, or heart rate less than 100 bpm/min; such infants might benefit more from

**Table 2: Comparison of clinical course and complications in the two study groups (N=37, for each study group)**

| Variable                                      | SI group    | nCPAP-only group | P     |
|-----------------------------------------------|-------------|------------------|-------|
| Need for MV within the first 72 hours of life | 3 (8.1%)    | 1 (2.7%)         | 0.304 |
| Duration of MV (h)                            | 38.67±16.17 | 34               | 0.456 |
| Duration of need to nCPAP (h)                 | 81.84±76.43 | 40.46±25.01      | 0.003 |
| Surfactant requirement                        | 7 (18.9%)   | 20 (54.1%)       | 0.003 |
| Duration of need to oxygen (d)                | 13.32±12.25 | 14.86±13.78      | 0.611 |
| CLD                                           | 9 (24.3%)   | 11 (29.7%)       | 0.794 |
| Pulmonary hemorrhage                          | 1 (2.7%)    | 0 (0%)           | 1.00  |
| Pneumothorax                                  | 1 (2.7%)    | 0 (0%)           | 1.00  |
| IVH (grade II or more)                        | 3 (8.1%)    | 1 (2.7%)         | 0.615 |
| NEC                                           | 2 (5.4%)    | 5 (13.5%)        | 0.430 |
| Length of hospital stay (d)                   | 37.05±10.18 | 45.35±14.24      | 0.005 |
| Death                                         | 0 (0%)      | 0 (0%)           | 1.00  |

Data are presented as mean±SD or number (%), where applicable. SI group: received sustained lung inflation followed by nasal continuous positive airway pressure, nCPAP-only group: received nasal continuous positive airway pressure alone, MV=mechanical ventilation, CLD=chronic lung disease, IVH=intraventricular hemorrhage, NEC=necrotizing enterocolitis, SD=Standard deviation

SI. In the study conducted by Lista *et al.*,<sup>[16]</sup> preterm infants with signs of respiratory distress in the delivery room who received SI followed by nCPAP had less need to and shorter duration of mechanical ventilation, less need to surfactant, a shorter duration of oxygen therapy, and a lower occurrence of BPD in survivors than infants who received nCPAP alone. The amount and duration of inflation pressure in the SI group was more than that of our study (25 cm H<sub>2</sub>O for 15 s), and also, this was repeated a second time based on predetermined criteria. Moreover, they used a mask that covered the mouth and nostrils, compared with using binasal prongs in our study; it might lead to different amounts of air leak around the devices and still affected the applied pressure to the airways more. Anyway, their findings regarding the need to surfactant were similar to our study. In another similar study which included infants with lower gestational age (extremely preterm infants), Lista reported that the need for MV in the first 72 hours of life was lower in the group of SI after early CPAP in the delivery room compared with the group of nCPAP alone, but the overall need of respiratory support and the occurrence of BPD were not decreased. In the SI group, the pneumothorax frequency and interstitial emphysema were higher than the control group. Although there was no significant difference, they believed that this finding deserved consideration.<sup>[14]</sup> In the present study, pneumothorax occurred in only one case in the SI group, but no one in the control group. Again, the difference was not statistically significant. In the study by El-Chimi *et al.*,<sup>[17]</sup> preterm infants who received SI followed by nCPAP at birth had less need to intubation in the delivery room or within the first 72 hours after birth compared to the infants who received positive pressure ventilation (PPV) via oral mask. The duration of nCPAP was also less in this group. Apart from the fact that compared to our study, infants in their study were less stable and needed PPV at birth, SI was delivered by a T-piece resuscitator, while PPV was applied using a bag and mask. Besides the effect of PEEP applied by T-piece resuscitator, the pressures are much better controlled using this device compared with the bag; this may be an

explanation for the differences in these results between the groups in their study.

Surprisingly, in our study, the duration of nCPAP was longer in the SI group than the control group. Less infants in the SI group received surfactant; it is not clear to us whether it can explain the above finding.

There are some systematic reviews and meta-analyses of studies on the effects of SI in premature infants. In 2020, Foglia *et al.*<sup>[9]</sup> published the results of a systematic review and meta-analysis of randomized clinical trials (RCTs) that compared the effects of SI (inflation time >5 seconds) versus standard resuscitation with either intermittent PPV or CPAP on the prevention of hospital mortality and common morbidities of preterm infants. Nine RCTs recruiting 1409 neonates with gestational age less than 37 weeks who needed resuscitation in the delivery room were included. There was no difference in the primary outcome of death before hospital discharge, although the risk of death in the first two days after birth was increased by applying SI. The need to mechanical ventilation and the occurrence of common morbidities, such as CLD or mortality, were also not significantly different. They included that routine use of SI for preterm infants after birth could not be supported. The Cochrane library also released in 2020, the results of a meta-analysis of nine studies on newborn infants who needed resuscitation with intermittent PPV, in which the use of an initial SI (>1 second duration) (including at the start of PPV) was compared with standard inflations (≤1 s). In this study, Bruschetti *et al.*<sup>[12]</sup> showed that in the delivery room or during a hospital stay SI without chest compression did not reduce the primary outcome of mortality better than intermittent ventilation. There was also no benefit of SI over intermittent ventilation in terms of secondary outcomes such as intubation rate, and rate or duration of any type of respiratory support or CLD. In the SI group, duration of mechanical ventilation was shortened; they discussed, however, that such finding should be cautiously interpreted, as the characteristics of the studies

might have influenced strongly rather than the intervention. They concluded that the use of SI could not be supported based on these evidences which had low or moderate quality. In 2021, Kapadia *et al.*<sup>[11]</sup> published the results of a systematic review and meta-analysis which compared strategies using 1 or more SI  $\geq 1$  second with intermittent inflations  $<1$  s for preterm infants at birth, on behalf of the International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support Task Force. Ten trials with 1502 enrolled preterm newborns were included. There were five studies on newborns who did not receive assisted ventilation at the beginning; in these studies, CPAP was initially applied and neonates received IPPV thereafter if needed. The length of SI in all of these studies was actually more than five seconds. Considering the primary outcome of death before discharge, no benefit was found in applying one or more SI of such duration for preterm infants at birth. Indeed, it might be increased among the subgroup born before 28 weeks' gestation. There was also insufficient evidence to determine the probable effect of this modality on death in the delivery room or death within the first two days of life and on other key morbidities, such as mechanical ventilation during hospitalization, air leaks at any time during initial hospitalization, CLD, IVH, and long-term neurodevelopmental, behavioral, or educational outcomes. There was very little conclusive evidence for death in the delivery room and low for other outcomes.

The amount and duration of inflation pressure, the use as prophylaxis or rescue and the frequency of applying SI, and the gestational age of the patient population are among the factors that can determine the efficacy and safety of this modality.

Studies on adult patients with ARDS have shown that the lung recruitment maneuver improved short-term outcomes of oxygenation and re-expansion of atelectatic regions of the lung. The overall mortality in these patients was not improved, most likely related to the role of severe inflammation in the pathogenesis of the disease.<sup>[13]</sup> RDS in infants is mostly due to the immaturity of respiratory units and surfactant deficiency rather than inflammation, which may make a difference in how this group of patients respond to SI. Considering that most of the previous studies in neonates focused on the efficacy of SI at birth in the delivery room, it can be suggested that more trials such as ours are designed to examine its role in the management of RDS in this age group. Moreover, these studies mainly evaluated short-term outcomes of infants who received SI; it is important that its effect on long-term outcomes of cardiopulmonary and neurodevelopment be also followed and evaluated.

## CONCLUSION

The results of our study showed that applying SI within the first minutes after birth in preterm infants with early signs of respiratory distress, mainly related to RDS, reduced the need for exogenous surfactant and the length of hospital stay while the duration of respiratory support by nCPAP

was increased. Further studies on the role of this modality in the management of RDS in neonates are suggested. In addition, its effect on long-term cardiopulmonary and neurodevelopment outcomes of these infants should be evaluated.

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## Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Isfahan University of Medical Sciences; the registration number was IR.MUI.MED.REC.1398.449. Informed consent was obtained from the parents before the delivery.

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## Conflicts of interest

There are no conflicts of interest.

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