ORIGINAL ARTICLE

Evaluation of intratracheal salbutamol effects in addition to surfactant in the clinical course of premature neonates with respiratory distress syndrome

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Background: In addition to surfactant deficiency, secretion of fluid from blood to the lungs and increase in the fluid content of the lung play significant roles in the pathogenesis of respiratory distress syndrome (RDS). Thus, we aimed to evaluate the effect of salbutamol (a beta-agonist) on fluid clearance from the lungs in neonates with RDS. **Materials and Methods:** This randomized controlled clinical trial included 82 neonates with RDS admitted to the neonatal intensive care units of Alzahra and Shahid Beheshti Hospitals of Isfahan University of Medical Science from 2017 to 2018. Patients were recruited through convenience sampling. They were randomized into two groups, using simple randomization: 42 were only treated with intra-tracheal surfactant (control group) and 40 with intra-tracheal surfactant plus salbutamol (intervention group). The two groups were compared regarding intubation surfactant administration and extubation (INSURE) failure, duration of nasal continuous positive airway pressure, intubation, oxygen therapy, morbidity, and mortality. **Results:** INSURE failure leading to mechanical ventilation occurred in 3 neonates in the control group and 2 in the intervention group ($P = 0.680$). Mean hospital length of stay did not differ significantly between groups ($P = 0.230$). Comparison of controls with the intervention group regarding complications and the incidence of morbidities revealed no statistically significant difference ($P > 0.05$). **Conclusion:** Findings of this study were not in favor of the routine use of salbutamol in neonates with RDS as it did not improve the course of the disease among newborns.

Key words: Albuterol, newborn, prematurity, respiratory distress syndrome, salbutamol

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INTRODUCTION

One of the main causes of disease complications and death in preterm infants is respiratory distress syndrome (RDS), which is the most common reason for newborn admission to the Neonatal Intensive Care Unit (NICU).[1] There are various new therapeutic modalities for treating RDS in neonates including the prescription of corticosteroid during pregnancy to accelerate fetal lung maturation, surfactant for premature neonates with RDS, and new modes of mechanical ventilation.[2]

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Surfactant replacement therapy is the main part of the management of RDS.[3] However, despite surfactant therapy many newborn infants especially more preterm ones, need advanced respiratory care and 20% of those surviving neonatal RDS may experience chronic lung diseases (CLDs).[4,5]

Prematurity of the lung due to surfactant deficiency is the leading cause of neonatal RDS. Furthermore, increased lung fluid and fluid secretion from blood to the lung significantly contribute to the pathogenesis of RDS.[6,7] Catecholamine secretion

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during labor is an important factor in lung clearance by inducing Na^+/K^+-ATPase pumps.[8] There is evidence that beta-agonists can significantly increase sodium channels' activity and sodium transition in the lung.[9] Multiple animal studies have assessed the effect of salmeterol, a long-acting beta-adrenergic receptor agonist, on lung fluid clearance and have reported that this beta-agonist can reduce lung fluid by 60% and increase lung fluid clearance.[10,11] Human studies on the effects of beta-agonists such as salbutamol on improving the clinical condition of ventilator-dependent very low birth weight (VLBW) neonates with lung diseases including bronchopulmonary dysplasia and respiratory distress showed significant efficacy of this treatment.[12] A study on 48 premature infants comparing the efficacy of intra-tracheal salbutamol and normal saline, reported that neonates in the saline group had a more extended hospitalization period.[13]

Intra-tracheal administration of some medications is a safe and effective method.[14] Studies evaluating the effects of intra-tracheal corticosteroids on neonatal lung diseases have reported that this method could reduce lung inflammation without any significant side effects.[15] Other studies have evaluated the effect of intra-tracheal budesonide on the management of neonatal RDS, showing the effectiveness of this treatment in improving mean air pressure, decreasing carbon dioxide (CO_2) retention, and diminishing the time to extubation.[14,16]

According to previous studies, salbutamol is an effective treatment for neonatal RDS and studies that used the medication via the intratracheal route have shown the efficacy of this method with very few side effects.[12,13] This study aimed to evaluate the effects of adding intra-tracheal salbutamol to surfactant on the clinical course of premature infants with RDS.

METHODS

Study design and subjects

This study is a single-blind randomized controlled clinical trial on neonates admitted to the NICUs of Alzahra and Shahid Beheshti Hospitals of Isfahan University of Medical Science (IUMS) from May 2017 to April 2018. The study was single blinded because the physicians who administered the intra tracheal drugs were aware from the type of intra tracheal drugs because we administered salbutamol after surfactant.

The sample size was calculated based on the formula mentioned below.[13]

$$n = 2\,(Z\alpha/2+Z_\beta)^2\,P\,(1-P)/(P_1-P_2)^2$$

$Z_1 = 1.96$, $Z_2 = 0.84$, $P_1 = 0.4$, $P_2 = 0.7$. Considering 80% as the power of the study, and confidence interval 95%. As a result, we needed a total of 80 patients and 40 newborns in each group calculated in this study.

The inclusion criteria were gestational age <34 weeks and 7 days and diagnosis of RDS based on clinical manifestations and chest X-ray findings (clinical manifestations: Respiratory distress, tachypnea, nasal flaring and grunting after birth; radiologic findings: Ground glass view, air bronchogram, and white lung).[13] Exclusion criteria included birth trauma, major congenital anomalies, perinatal asphyxia, 5-min Apgar score ≤3, severe metabolic acidosis at birth, positive blood culture, and parents' unwillingness to continue the study.

Neonates with RDS were treated with nasal continuous positive airway pressure (NCPAP), and arterial blood gas (ABG) test was performed 30 min later. Neonates who needed more than 40% FiO_2 despite receiving 6 cm H_2O NCPAP, were treated with intra-tracheal surfactant.[17] Mechanical ventilation was considered in babies with Continuous Positive Airway Pressure (CPAP) failure (who needed more than 40%–60% FiO_2 despite receiving 6 cm H_2O CPAP) and excessive work of breathing and severe respiratory acidosis.[18]

Surfactant (CUROSURF®, Chiesi Farmaceutici, Italy) was administered with an initial dose of 2.5 ml/kg and a subsequent dose of 1.25 ml/kg, 8 h after the first dose if needed. Patients who required FiO_2>30% were treated with up to 4 repeated doses of surfactant during the first 72 h of life.[19] The NCPAP pressure was reduced sequentially when the patients required FiO_2 <30% and NCPAP was discontinued in neonates if receiving NCPAP of 4 cm H_2O and FiO_2 <30% if they did not have increased work of breathing, substantial apnea, and bradycardia.[20]

Most studies used nebulized salbutamol with a dose of 0.15 mg/kg, but we wanted to use it intatrachealy based on Dehdashtian's *et al*. study.[13,20] We conducted a pilot study and followed up 10 newborns with RDS after intra-tracheal administration of salbutamol, and we found that 7 of them had a heart rate above 200, so we decided to give this drug with a lower dose (0.1 mg/kg). Patients who were treated with surfactant were randomly divided into two groups based on a random allocation system, using simple randomization (according to their medical file number either singular or plural).

After surfactant administration, patients in the first group (intervention group) received 0.1 mg/kg salbutamol (Asthalin, Cipla Ltd, India), and those in the second group (control group) did not receive anything. Normal saline (injection type) at a dose of 0.5 ml/kg was used for the

dilution of salbutamol into the proper volume. Salbutamol was administered immediately after surfactant by the same intra-tracheal tube without a nebulizer.[13]

We evaluated the duration of NCPAP therapy, mechanical ventilation, and oxygen therapy, as well as morbidities including apnea (minor and major), necrotizing enterocolitis (NEC), pneumothorax, bleeding, sepsis, patent ductus arteriosus (PDA), and CLD. Furthermore, before and 30 min after the intervention heart rate and mean blood pressure were measured. Moreover, after the intervention, hospital length of stay, mean time to achieve full enteral feeding (120 cc/kg), and mortality were recorded. Discharge criteria were as follows: (1) medical stability (treatment plan for all medical condition was in place, would not require frequent changes); (2) respiratory stability; and (3) home stability (stable home and family setting).[21]

Statistics

Data were entered into the Statistical Package for the Social Sciences (SPSS) software (SPSS 25.0 SPSS crop., Chicago, IL, USA) and analyzed for reporting quantitative and qualitative data, we used mean ± standard deviation and number or percent, respectively. For analytical analysis, the independent-samples *t*-test (parametric variables), Mann–Whitney test (nonparametric variables), and Chi-square test were used for comparison between groups. Due to that the data was not intervening variable, advanced statistical tests were not used for adjustment. A two-sided α level of 0.05 was used to assess statistical significance.

Ethics statement

The study was approved by the ethical committee of IUMSs (Code: IR.MUI.REC.1396.3.692). Furthermore, the study was explained to the neonates' parents, and a written informed consent was obtained.

RESULTS

Overall, 87 neonates were assessed for eligibility. Of these, 3 were excluded because they did not meet the inclusion criteria, and 84 were equally randomized into two groups, 42 newborns in each group. Two neonates in the intervention group did not receive the allocated intervention because the parents refused to continue the study [Figure 1]. Three neonates in the intervention group and two in the control group died ($P = 0.670$).

Of the 82 neonates with RDS evaluated in this study, 40 were in the intervention group and 42 in the control group. Patients in both groups were comparable regarding gestational age, gender, type of delivery, maternal use of corticosteroids, and 5-min Apgar score, as well as birth weight, height, and head circumference [Table 1].

Table 1: Patient's general characteristics

Variables	Intervention group	Control group	*P*
Gestational age* (weeks)	31.67±2.05	31.78±1.76	0.790
Gender**, *n* (%)			
Male	23 (57.5)	21 (50)	0.510
Female	17 (42.5)	21 (50)	
Type of delivery**, *n* (%)			
Normal vaginal delivery	6 (15)	4 (9.5)	0.510
Cesarean section	34 (85)	38 (90.5)	
Receiving corticosteroid by the mother**, *n* (%)			
Yes	25 (62.5)	29 (69)	0.640
No	15 (37.5)	13 (31)	
Birth weight* (g)	1756±506.06	1719.64±472.38	0.730
Birth height* (cm)	42.73±4.14	42.47±3.93	0.770
Head circumference*(cm)	30.1±3.14	30.21±1.98	0.840
5-min Apgar score*	6.8±1.55	6.92±1.21	0.680

*Independent-samples *t*-test; **Chi-square test

The mean frequency of surfactant administration was higher in the control group compared to the intervention group; however, the difference was not statistically significant ($P = 0.940$). Three patients in the control group and two patients in the intervention group had intubation surfactant administration and extubation failure and needed mechanical ventilation ($P = 0.680$). Mean duration of NCPAP therapy in days was lower in the intervention group compared to control group but was not statistically significant (42.95 ± 34.84 vs. 46.14 ± 48.28, $P = 0.206$).

The mean duration of oxygen therapy in hours was lower in the intervention group compared to the control ones (103.28 ± 20.9 vs. 55.95 ± 23.11, $P = 0.18$) but was not statistically significant. The mean hospital length of stay in days was lower in the intervention group in comparison to the control group (12.87 ± 8.2 vs. 15.85 ± 13.6, $P = 0.23$) although, it was not statistically important, also mean time to achieve full enteral feeding was lower in the intervention group but it was not statistically important between groups [Table 2].

Mean blood pressure and mean heart rate were not significantly different between the intervention and control groups, both before and after the intervention [Table 2]. The incidence of apnea, pneumothorax, pulmonary hemorrhage, sepsis, NEC, PDA, and CLD were not significantly different between groups [Table 3]. Three neonates in the intervention group and two in the control group died ($P = 0.670$).

DISCUSSION

This study assessed the effects of adding salbutamol to surfactant in neonatal RDS based on the hypothesis that using salbutamol in addition to surfactant can increase the absorption of lung fluid, which is affected by the

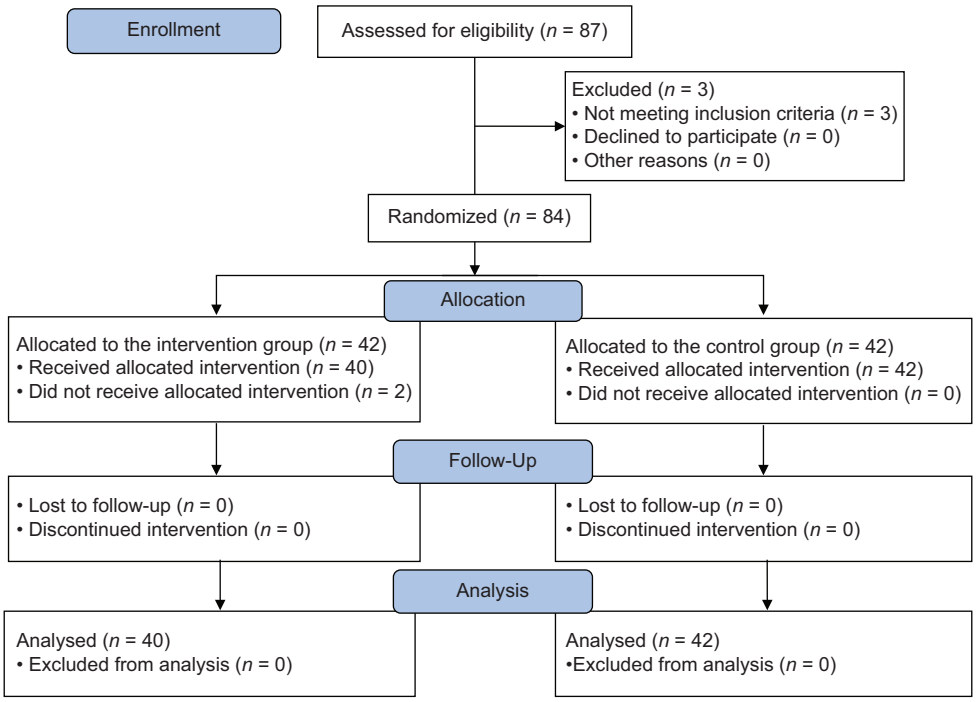

Figure 1: Details of patient enrollment, intervention allocation, and analysis

Table 2: Comparison of intubation surfactant administration and extubation failure, frequency of surfactant administration, duration of nasal continuous positive airway pressure and oxygen therapy, hospital length of stay between the intervention and control groups

Variables	Intervention group	Control group	*P*
INSURE failure* (mechanical ventilation requirement), *n* (%)	2 (5)	3 (7.1)	0.680
Frequency of surfactant administration*	1.42±0.6	1.5±0.52	0.940
Duration of NCPAP* (hours)	42.95±34.84	46.14±48.28	0.206
Duration of oxygen therapy* (hours)	55.95±23.11	103.28±20.49	0.180
Hospital length of stay* (days)	12.87±8.20	15.85±13.6	0.230
Time to achieve full enteral feeding* (days)	6.97±2.03	8.19±2.7	0.570
Blood pressure before* (mmHg)	38.87±8.94	37.76±6.78	0.670
Blood pressure after 30 min (mmHg)	38.97±3.89	37.73±3.09	0.115
Heart rate before* (bpm)	141.15±7.93	140.26±6.97	0.590
Heart rate after 30 min* (bpm)	147.0±11.77	143.76±5.7	0.116

*Independent-samples *t*-test. NCPAP=Nasal continuous positive airway pressure; INSURE=Intubation surfactant administration and extubation

neonatal clinical course. Although the findings of this study showed that neonates who were treated with salbutamol plus surfactant had a lower rate of NCPAP failure and mechanical ventilation requirement, these differences were not statistically significant.

Limited studies have evaluated the effects of salbutamol plus surfactant in neonatal RDS, especially administered through the intratracheal route. Previous studies showed that not only can beta-agonists reduce lung fluid, but also have a crucial role in improving ABG.[10] Beta-agonists can induce Na^+/K^+-ATPase channels in the lung. Lung fluid absorption occurs when Na^+ is actively transported from lung air spaces through the respiratory epithelium into the interstitium by the activation of Na^+/K^+-ATPase channels.[22] There is evidence that beta-agonists can induce cyclic adenosine monophosphate and consequently increase lung fluid clearance.[23] Beta-agonists can reduce alveolar inflammation, improve endothelial and epithelial barrier function, increase alveolar fluid clearance, and improve epithelial repairment.[11,24]

To the best of our knowledge, there is only one similar study that has compared the effect of intra-tracheal salbutamol plus surfactant with intra-tracheal normal saline and surfactant on neonates with RDS and has shown no differences between groups with respect to the need for mechanical ventilation, NCPAP failure, and duration NCPAP and oxygen therapy requirement.[13] In this study, only the length of hospital stay was significantly lower in neonates who received salbutamol and surfactant.[13] These findings were in line with the results of our study, except for the hospital length of stay which was similar in both groups.

Some studies have evaluated the effect of salbutamol in neonates with respiratory distress; nevertheless, most of them have used inhalational instead of intra-tracheal salbutamol. Lee *et al*. compared the effect of single-dose salbutamol or ipratropium bromide and placebo

Table 3: Comparing the incidence of complications between the intervention and control groups

Variables	Intervention group, *n* (%)	Control group, *n* (%)	*P*
Death*	3 (7.5)	2 (4.8)	0.670
Apnea*	5 (12.5)	8 (19)	0.540
Pneumothorax*	1 (2.5)	2 (4.8)	0.580
Pulmonary hemorrhage*	2 (5)	2 (4.8)	0.960
Sepsis*	1 (2.5)	2 (4.8)	0.580
NEC*	1 (2.5)	1 (2.4)	0.970
PDA*	2 (5)	3 (7.1)	0.680
CLD*	0	1 (2.4)	0.320

*Chi-square test. NEC=Necrotizing enterocolitis; PDA=Patent ductus arteriosus; CLD=Chronic lung disease

administered by metered-dose inhaler at intervals of more than 8 h in 2–3 consecutive days on ventilator-dependent infants. This study reported that both salbutamol and ipratropium bromide were able to significantly increase PaO_2 and decrease $PaCO_2$ compared to placebo. The ventilator efficient index improved in salbutamol and ipratropium bromide groups in comparison with the placebo, but this improvement was not statistically significant. Tachycardia, hypotension, or hypertension were not observed in participants of this study.[25] In another randomized clinical trial on VLBW neonates under ventilation, one group received 100 µg/6 h salbutamol and the other 12 µg/12 h formoterol by metered-dose inhaler for 2 consecutive days. The minute volume increased by 26% and 22% in the salbutamol and formoterol groups, respectively. Mean static compliance increased in both groups. This study suggested that both salbutamol and formoterol had equivalent effects on increasing minute volume, heart rate, and tidal volume in ventilated infants. This study did not show any tachyphylaxis during the 1st week after treatment in participants.[26] Armangil *et al*. evaluated the effect of nebulized salbutamol (4 ml) versus placebo (0.9% normal saline) in 54 neonates with transient tachypnea of the newborn. They demonstrated that mean pH, partial pressure of arterial oxygen, and partial pressure of arterial CO_2 better improved in the salbutamol group compared to the placebo group and that the duration of hospitalization was lower in the salbutamol group.[20] Monzo *et al*. assessed the effect of nebulized salbutamol (0.15 mg/kg) on 46 neonates with transient tachypnea of newborns and showed significant improvement of lung function and tachypnea with salbutamol.[27] Another study including 148 neonates with transient tachypnea of the newborn investigated the effect of inhaled salbutamol versus normal saline and reported that duration of hospitalization, heart rate, FiO2, and O2 saturation was significantly higher in neonates of the salbutamol group. No complication was reported with this treatment.[28] Moreover, mortality and other complications were comparable between the two groups, similar to a previous study.[13]

A similar study by Dehdashtian *et al*. evaluating intra-tracheal salbutamol showed the efficacy of this intervention on decreasing the duration of NCPAP, NCPAP failure, and the need for mechanical ventilation.[13] Our findings were mostly consistent with the results of this study; however, we found that intra-tracheal salbutamol was not effective in neonatal RDS. This difference can be justified by the lower dose of salbutamol in our study. We decided to use a lower dosage of salbutamol because of its effects on heart rate and blood pressure. Most of the other studies that treated bronchopulmonary diseases had used higher doses of salbutamol. Furthermore, in Dehdashtian's *et al*. study, neonates in the control group received normal saline in addition to surfactant, but in our study, the effects of surfactant without dilution with normal saline and surfactant plus salbutamol were compared. Dilution of surfactant with normal saline could have reduced its efficacy in the control group and made the difference between the two groups statistically significant. The way of exposure to salbutamol in our study was similar to other studies that prescribed salbutamol after surfactant through the intra-tracheal route without re-intubation. To determine the exact effects of intra-tracheal salbutamol on neonates with RDS, further studies using higher doses of salbutamol and surfactant and considering confounding factors are required.

This study has its strengths and limitations. One of the strengths of this study was prescribing intra-tracheal salbutamol which is a new route of administration with fewer complications; a few studies have used this method. The limitation of this study was its small sample size which is not adequate for generalizing our findings. Future studies should be designed with a larger sample size and consider other confounding variables to assess the exact effects of intra-tracheal salbutamol in combination with surfactant.

CONCLUSION

According to this study, prescribing low dose intra tracheal salbutamol accompanied by surfactant cannot significantly alter the clinical course in neonatal RDS.

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Conflicts of interest
There are no conflicts of interest.

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