A Randomized Clinical Trial of Intratracheal Administration of Surfactant and Budesonide Combination in Comparison to Surfactant for Prevention of Bronchopulmonary Dysplasia

Manizheh Mostafa Gharehbaghi¹*, Shalale Ganji², Majid Mahallei³

¹Professor of pediatrics & neonatology. Pediatric Health Research Center. Tabriz University of Medical Sciences. Tabriz. Iran.

²Assistant Professor of Pediatrics & Neonatology. Tabriz University of Medical Sciences

³Assistant Professor of Pediatrics & Neonatology. Tabriz University of Medical Sciences

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*Corresponding author: gharehbaghimm@yahoo.com

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Abstract

Background: Bronchopulmonary dysplasia (BPD) remains a major problem in preterm infants that occurs in up to 50% of infants who are born at less than 28 weeks gestational age. The inflammation plays an important role in the pathogenesis of BPD. This study was conducted to evaluate the efficacy of intratracheal budesonide administration in combination with surfactant in the prevention of BPD in preterm infants.

Materials and methods: In a randomized clinical trial, 128 preterm infants at less than 30 weeks gestational age and birth weight less than 1500 g were studied. All of them had respiratory distress syndrome (RDS) and needed surfactant replacement therapy. They were randomly allocated in two groups, surfactant group (n=64) and surfactant+budesonide group (n=64). Neonates in surfactant group received intratracheal Curosurf 200mg/kg/dose. Patients in surfactant+ budesonide group treated with an intratracheal instillation of a mixed suspension of budesonide 0.25 mg / kg and Curosurf 200mg/kg/dose. Neonates were followed till discharge for the primary outcome which was BPD and secondary outcome
including sepsis, patent ductus arteriosus (PDA), retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC).

**Results:** The mean gestational age and birth weight of studied neonates were 28.3±1.6 weeks and 1072±180 grams, respectively. The demographic characteristics and RDS score were similar in the two groups. BPD occurred in 24 (37.5%) neonates in surfactant + budesonide group and 38 (59.4%) neonates in surfactant group, p=0.04. Hospital stay was 29.7±19.2 (median 30) days in surfactant group and 23.3±18.1 (median 20) days in surfactant + budesonide group, p=0.05. The rate of sepsis, PDA, ROP and NEC were not significantly different in two groups.

**Conclusion:** Based on our findings, the use of budesonide in addition to surfactant for rescue therapy of RDS in preterm infants decreases the incidence of BPD and duration of respiratory support significantly. Large adequately powered clinical trials with long term safety assessment are needed to confirm our findings before its routine use can be recommended.

Key words: respiratory distress syndrome, bronchopulmonary dysplasia, surfactant, budesonide, preterm infants

**Introduction**

Respiratory distress syndrome (RDS) in preterm infants is caused by a deficiency of pulmonary surfactant which is necessary to reduce surface tension at alveoli. Increased surface tension, if untreated, may cause progressive airway collapse

The benefits of maternal antenatal corticosteroids in lung maturity had been reported in previous studies. Use of antenatal corticosteroids and exogenous surfactant improves the survival of preterm infants with RDS. Bronchopulmonary dysplasia (BPD) remains a major problem in preterm infants that occurs in up to 50% of infants who are born at less than 28 weeks gestational age. BPD risk factors include lower gestational age and birth weight, male gender, white race and genetic factors, perinatal asphyxia, patent ductus arteriosus and mechanical ventilation parameters.

Since, there is marked variation among medical centers in BPD rates, it is suggested that specific care practice can modify BPD occurrence. There are preclinical and clinical studies that suggest the role of inflammatory reactions in pathogenesis of RDS and BPD. Researchers showed inflammatory mediator release in response to pulmonary toxins which
include oxidants, free radicals, hypoxia, infection or volutrauma. BPD appears to be induced by pro-inflammatory cytokines, chemokines and proteinase mediated events. Corticosteroids as anti-inflammatory agents have been studied to prevent BPD. Using systemic corticosteroids at first month of life may increase the risk of long term side effects in preterm infants. Because of adverse neuro-developmental effects of systemic steroids, there is a tendency to research about airway administration of steroids. Intratracheal instillation is a better way to administer corticosteroids with direct drug introduction into alveolar space and the least systemic adverse effects. Budesonide is a corticosteroid with a local anti-inflammatory effect that has 10-fold stronger potency in reducing pro-inflammatory cytokine release including tumor necrosis factor (TNF) and interleukin 1-b. Budesonide has well absorption and persistence in lungs because of budesonide ester formation at the carbon 21-hydroxyl group and slow free budesonide release. So, budesonide is superior to other corticosteroids for intratracheal administration. A systematic review of 20 trials of airway administration of corticosteroids (16 trials of inhaled corticosteroids and 4 trials of instillation of steroids) from 1993 to 2016 indicated that it is associated with a lower likelihood of BPD than placebo without benefit with respect to mortality. BPD or mortality rate was significantly lower only in the group treated with budesonide. The duration, dose, type, the inhalation or instillation of steroids using surfactant as carrier were inconsistent across studies. The duration of inhalation of corticosteroids ranged from 3 to 29 days and the first delivery time ranged from 12 hours to 14 days. Since the Meta analyses showed the airway administration of corticosteroids by instillation is still regarded as an open research area, we conducted this study to evaluate the efficacy intratracheal budesonide administration in combination with surfactant in the prevention of BPD in preterm infants.

Materials and methods

This randomized clinical trial was conducted in neonatal intensive care unit of AL Zahra hospital which is a tertiary, university referral center in North West of Iran. The study was approved by Ethic committee of Tabriz University of Medical Sciences by code IR.TBZMED.REC. 1397.041 and registered in Iranian Registry of Clinical Trials (IRCT) by number IRCT 20100512003915N20. Parental informed written consent was obtained before patient enrollment. Considering the findings of Yeh and coworkers in 2015 as a default and considering reducing the rate of BPD from 66% to 42% in budesonide group with power 80% and alpha 0.05 we estimate that 64 cases are needed for each group. With considering the
dropout rate we estimate 67 neonates for each group. Infants were excluded for major congenital anomalies, birth asphyxia (Apgar score less than 4 at 5 minutes after birth) and need to prolonged resuscitation; and lethal cardiopulmonary disorder.

Inborn preterm infants at less than 30 weeks gestational age and birth weight less than 1500 g who had RDS and need surfactant replacement therapy from July 2018 to April 2019 were eligible. Gestational age was determined by first trimester ultrasound examination and confirmed by neonatal examination using Ballard gestational age scoring. At birth, all neonates received nasal continuous positive airway pressure (CPAP) 5-6 cm H$_2$O by infant T piece resuscitator (Fisher& Paykel Health Care, Auckland, New Zealand) and transferred to NICU while covered by plastic bag in portable incubators. In the neonatal intensive care unit, CPAP was administered through short bilateral nasal prongs, intermittently with a nasal mask. Distending pressure was generated by a variable flow nasal CPAP device and PEEP 5-7 cm H$_2$O and flow 6-7 litter/min (Fisher& Paykel Health Care limited, New Zealand). The diagnosis of RDS was based on clinical signs and symptoms and confirmed by radiologic findings. RDS severity was determined by using RDS score. Surfactant was given to infants who met clinical and radiologic criteria for respiratory distress syndrome (RDS) as INSURE treatment method within 2-6 hours of life. Targeted Spo2 was 90-92%. Enrolled patients were randomly allocated in two groups by random number list generated by random number generator in sequentially numbered, opaque, sealed and stapled envelopes. Neonates in surfactant group received intratracheal Curosurf (Poractant alpha, Chiesi Farmaceutici, Italy) 200mg/kg/dose (2.5 ml/kg /dose) after premedication with fentanyl 1-2 mic/ kg. Patients in surfactant + budesonide group treated with an intratracheal instillation of a mixed suspension of budesonide (pulmicort nebulizing suspension, AstraZeneca AB, Sodertalje, Sweden) 0.25 mg / kg(0.5 cc/kg) and Curosurf 200mg/kg/dose (2.5 ml/kg /dose). An independent nurse prepared syringes with surfactant and surfactant+ budesonide and put them into envelopes according to the allocation orders. The envelopes opened just before the instillation. Surfactant replacement therapy was done in the first 2 hours of life in both groups. Surfactant administered as RDS rescue treatment to infants receiving CPAP at a pressure >5 cm H$_2$O who needed a FiO$_2$ more than 30% to maintain oxygen saturation between 88% and 92%. Following surfactant administration, when the spontaneous respirations resumed, and after adequate heart rate and oxygen saturation establishment, endotracheal tube removed and the infants weaned to NCPAP. Endotracheal intubation was reserved for infants who had severe respiratory distress, apnea or ineffective respiratory effort or hemodynamic instability. The
second dose of surfactant was administered to infants with persistent increased work of breathing and FiO₂ requirements more than 30% while other problems have been excluded.

CPAP was weaned in increments of 1 cm H₂O every 12-24 hours when infants were stable by considering work of breathing, respiratory rate, oxygen requirement and underlying lung pathology. The infants who had weaned from CPAP with mild tachypnea were supported by heated humidified nasal cannula (HFNC) 3-4 liter / min delivered by binastral prongs. We considered CPAP failure when the extubated infant developed respiratory distress and need Fio₂ more than 0.4 for maintaining o₂ saturation more than 90%. Arterial blood gas parameters recorded at admission and at 6 hours intervals after surfactant administration. The neonatologist who managed the neonates was blind about the patients group. After 28 days of birth, another independent researcher who was blind about patients groups measured the patient's oxygen dependency. Infants who had continued to receive oxygen considered as having BPD. For all enrolled neonates a detailed questionnaire was completed.

Premature rupture of membranes (PROM) refers to a rupture of membranes prior to the onset of labor and before 37 weeks’ gestation. Clinical chorioamnionitis was diagnosed in the setting of maternal fever (≥38 °C) and at least two of the following: maternal leukocytosis (> 15,000 cells/mm³), tachycardia (>100bpm), fetal tachycardia (>160 bpm), uterine tenderness, stained or fuel smelling amniotic fluid. Decolman or placental abruption is premature separation of the placenta from the uterus present with bleeding, uterine contractions and fetal distress. Cranial ultrasound examination was performed on days 5 to 7 of birth for the diagnosis of intraventricular hemorrhage (IVH) by an experienced pediatric radiologist. Patent ductus arteriosus (PDA) was diagnosed based on clinical signs and confirmed by echocardiography performed by an expert pediatric cardiologist. The primary outcome was bronchopulmonary dysplasia (BPD). BPD was defined as the need for supplemental oxygen for at least 28 days and its severity determined at 36 weeks of gestation age based on the fraction of inspired oxygen. The secondary outcome included the total days of hospital stay and other complications of prematurity including sepsis, necrotizing enterocoloitis (NEC), PDA, pulmonary hemorrhage, IVH and retinopathy of prematurity (ROP). Sepsis was defined as either positive blood culture sepsis or suspected sepsis if septic screen was positive in presence of clinical signs and symptoms but negative blood culture.

After pupilary dilation, the retinas were examined through indirect ophthalmoscope. ROP was classified according to the international classification.
The statistical analyses were performed by a person who did not involve in the diagnosis and treatment of infants using SPSS version 16.0. Quantitative data were presented as mean ± standard deviation (SD) and qualitative data as frequency and percent. Categorical data were analyzed by chi-square test or Fisher's exact test. Normally distributed quantitative variables were compared by student's t-test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 128 preterm neonates were enrolled in this study, of which 64 were allocated to surfactant + budesonide group. Seventy eight neonates (61%) were boys. The mean gestational age and birth weight of studied neonates were 28.3±1.6 weeks and 1072±180 grams respectively. The most common maternal risk factor for preterm labor was preeclampsia, 35 (27%) cases. There wasn’t any case of chorioamninitis. The demographic characteristics were similar in the two groups (table 1).

Mechanical ventilation was needed in 28 (43.7%) neonates in surfactant group and 24 (37.5%) neonates in surfactant +budesonide group, p=0.63. The maximum respiratory support types and the mean duration of each of them are presented in table 2. The mean duration of respiratory support was significantly longer in surfactant group in comparison with surfactant+budesonide group (mechanical ventilation 2.8±0.6 vs. 0.8±0.1 days, p=0.006, nasal continuous positive airway pressure 5.2±3.0 vs. 4.0±3.5 days, p=0.04 and high flow nasal cannula 7.7±0.9 vs.4.1±0.5 days, p=0.001). BPD was detected in 62 (48.4%) neonates that 38 (61.3%) neonates were in surfactant group and 24 (38.7%) neonates in surfactant +budesonide group, p=0.04. The severity of BPD was mild in 27 (71.1%), moderate in 8 (21.1%) and severe in 2 (5.3%) neonates in surfactant group vs. mild in 20 (83.3%) and moderate in 4 (16.7%) neonates in surfactant +budesonide group.

Repeated doses of surfactant replacement therapy was used in 34 (26.5%) of studied neonates that 24 (37.5%) were in surfactant group and 10 (15.6%) in surfactant+budesonide group, p=0.01. The observed complications of prematurity are presented in table 3.

Vitamin A was used in 59 (90.6%) neonates in both groups for BPD prevention at first 4 weeks of life. Caffeine was used in all neonates in both groups. Any neonate has received systemic steroids as acceleration of extubation or BPD management.
Preterm infants with gestation age less than 30 weeks were assessed for eligibility

N=235

Exclusion (17)
Congenital anomalies, N=8
Parental refuse consent
N=5
Death at first 24 hours of birth, N=3
Prolonged resuscitation
N=1

Neonates included
N=217

No surfactant therapy
N=92

Enrolled neonates
N=128

Surfactant group
N=64

Surfactant + budesonide group
N=64

Death
N=9

BPD
N=38

BPD
N=24

Death
N=6
Flow chart of inclusion

Table 1- Demographic characteristics of preterm infants in the two groups

|                                      | Surfactant group N=64 | Surfactant+ budesonide group N=64 | P value |
|--------------------------------------|-----------------------|-----------------------------------|---------|
| Gender                               |                       |                                   |         |
| Male, n (%)                          | 40(62.5)              | 38(59.3)                          | 0.85    |
| Gestational age, wk                  | 28.4±1.5              | 28.2±1.7                          | 0.38    |
| Birth weight, gr                     | 1089±168              | 1055±192                          | 0.27    |
| Cesarean delivery, n (%)             | 53 (82.8)             | 52(81)                            | 1       |
| Maternal preeclampsia, n (%)         | 21(32.8)              | 14(21.8)                          | 0.21    |
| PROM, n (%)                          | 16(25)                | 12(18.7)                          | 0.52    |
| Placental abruption, n (%)           | 4(6.2)                | 6( 9.3)                           | 0.51    |
| Maternal diabetes mellitus, n (%)    | 1(1.5)                | 2(3.1)                            | 0.51    |
| Maternal hypothyroidism, n (%)       | 6(9.3)                | 8 (12.5)                          | 0.57    |
| Multiple gestations, n (%)           | 26(40.6)              | 18(28.1)                          | 0.13    |
| Maternal age, yr                     | 28.2±6.7              | 29.7±5.7                          | 0.18    |
|                                      | Surfactant group N=64 | Surfactant+ budesonide group N=64 | P value |
|--------------------------------------|------------------------|-----------------------------------|---------|
| Mechanical ventilation (MV), n (%)   | 28(43.7)               | 24(37.5)                          | 0.62    |
| NCPAP, n (%)                         | 61(95.3)               | 59 (92.1)                         | 0.47    |
| HFNC, n (%)                          | 54 (84.3)              | 52(81.2)                          | 0.46    |
| Duration of MV, d                    | 2.8±0.6                | 0.8±0.1                           | 0.006   |
| Duration of CPAP, d                  | 5.2±3.0                | 4.0±3.5                           | 0.04    |
| Duration of HFNC, d                  | 7.7±0.9                | 4.1±0.5                           | 0.001   |
| The number of surfactant therapy     |                        |                                   | 0.01    |
|   | Fio₂ | 1h after treatment | 24 h after | PH | Admission | 6 h after treatment | P CO₂ | Admission | 6 h after treatment | HCO₃ | Admission | 6 h after treatment |
|---|------|-------------------|------------|----|-----------|-------------------|-------|------------|-------------------|------|------------|-------------------|
| 1 | 40(62.5) | 0.37±0.14 | 0.30±0.08 | 7.21±0.07 | 50.7±9.8 | 20.0±3.07 | 20.4±2.38 |
| 2 | 20 (31.2) | 0.35±0.14 | 0.26±0.07 | 7.21±0.09 | 50.3±13.7 | 20.2±3.35 | 19.8±3.56 |
| 3 | 4 (6.2) | 0.37±0.14 | 0.30±0.08 | 7.32±0.09 | 38.0±10.9 | 20.4±2.38 | 19.8±3.56 |

Fio₂: 1h after treatment: 0.37±0.14 vs 0.30±0.08, 24 h after: 0.35±0.14 vs 0.26±0.07

PH: Admission: 7.21±0.07 vs 7.31±0.07, 6 h after treatment: 7.21±0.09 vs 7.32±0.09

P CO₂: Admission: 50.7±9.8 vs 40.6±8.5, 6 h after treatment: 50.3±13.7 vs 38.0±10.9

HCO₃: Admission: 20.0±3.07 vs 20.4±2.38, 6 h after treatment: 20.2±3.35 vs 19.8±3.56
Table 3. Complications of prematurity in two groups

|                          | Surfactant group N=64 | Surfactant+ budesonide group N=64 | P value |
|--------------------------|------------------------|----------------------------------|---------|
| BPD, n (%)               | 38 (59.4)              | 24 (37.5)                        | 0.04    |
| Hospital stay, d (median) | 29.7±19.2              | 23.3±18.1                        | 0.05    |
| PDA, n (%)               | 17 (26.5)              | 13 (20.3)                        | 0.20    |
| Pneumothorax, n (%)      | 3 (4.6)                | 1 (1.5)                          | 0.16    |
| Pulmonary hemorrhage, n (%) | 5 (7.8)              | 3 (4.6)                          | 0.24    |
| Sepsis, n (%)            | 25 (39)                | 21 (32.8)                        | 0.23    |
| ROP, N (%)               | 3 (4.6)                | 2 (3.1)                          | 0.32    |
| NEC, n (%)               | 4 (4.6)                | 2 (3.1)                          | 0.20    |
| Mortality, n (%)         | 9 (14)                 | 6 (9.3)                          | 0.29    |

We haven’t any case of gastrointestinal bleeding, intestinal perforation, and hypertrophic cardiomyopathy in our studied neonates. We haven’t assessed growth failure in studied neonates after discharge.

**Discussion**
In our study intratracheal administration of budesonide + surfactant in comparison with solitary surfactant replacement therapy was associated with reduced BPD rate in preterm infants who had RDS. Patients treated with budesonide + surfactant required less frequently repeated doses of surfactant replacement therapy, less duration of respiratory support and hospital stay. Similar to our findings, in a clinical trial conducted in United States and Taiwan, 265 very low birth weight infants with severe RDS who required mechanical ventilation within first hour of birth were studied. They reported a significantly lower incidence of BPD or death in patients treated by surfactant and budesonide compared with surfactant only. They found a fewer doses of required surfactant replacement therapy and lower interleukin levels in tracheal aspirates in these infants. The incidence of IVH, NEC, ROP and sepsis were comparable in two groups, similar to our study. In contrast to our finding, they reported a significantly lower incidence of PDA without significant difference in duration of mechanical ventilation or oxygen therapy. In another study, 116 very low birth weight infants with severe RDS that need mechanical ventilation after birth were assessed. Early tracheal instillation of budesonide using surfactant as a vehicle resulted in lower mean airway pressure (MAP) on day 1 and 3, lower PCO₂ and oxygen index during first 3 days, lower death or chronic lung disease.

The exact mechanism by which the intra tracheal budesonide may reduce the incidence of BPD is unknown. Li et al reported that intra tracheal instillation of budesonide +surfactant in rabbits could increase the alveolar area, decrease the alveolar wall thickness, increase density of lamellar bodies protein levels in type II epithelial cells of pulmonary alveoli. It is suggested that surfactant act as a vehicle that facilitate the delivery of budesonide to the lung periphery, enhance its solubility and absorption. It is showed that intratracheal budesonide is associated with improved gas exchange, oxygenation index, reduced pulmonary edema and inflammation. Yeh and coworkers showed remaining budesonide in the lungs for up to 8 hours after intra tracheal administration and estimate its 5-10% remaining in the lungs by 1 week. These effects account for diminished rate, duration of respiratory support, and the mechanical ventilation induced lung injuries. The fraction of inspired oxygen 24 hours after treatment and the need for repeated doses of surfactant replacement therapy were significantly lower in surfactant+ budesonide group in our study.

Since the blood gas analyses after surfactant administration were not significantly different among two studied groups, we suggest our used volume of budesonide couldn't dilute surfactant at the liquid air surface.
No serious side effects including hyperglycemia were seen. This study is the first single center trial in our country about prevention of BPD by budesonide + surfactant combination. We haven't assessed the long term possible side effects of budesonide + surfactant replacement therapy in preterm infants. It is recommended future studies with large number of patients and their long term follow up to determine possible side effects. The limitations of our study were small sample size, short term follow up and lack of long term neuro-developmental assessment.

In conclusion, based on our study findings, the intratracheal administration of surfactant and budesonide combination improve short term outcome in preterm infants with respect to incidence of BPD, need to repeated doses of surfactant, duration of assisted ventilation and hospitalization. Large adequately powered clinical trials with long term safety assessment are needed to confirm our findings before its routine use can be recommended.

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