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

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ABSTRACT

Objectives: Bronchopulmonary dysplasia (BPD) remains a major problem in preterm infants occurring in up to 50% of infants born at < 28 weeks gestational age. 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 a surfactant in preventing BPD in preterm infants. ***Methods***: In a randomized clinical trial, 128 preterm infants at < 30 weeks gestational age and weighing < 1500 g at birth were studied. All had respiratory distress syndrome (RDS) and needed surfactant replacement therapy. They were randomly allocated into two groups; surfactant group (n = 64) and surfactant + budesonide group (n = 64). Neonates in the surfactant group received intratracheal Curosurf 200 mg/kg/dose. Patients in the surfactant + budesonide group were treated with intratracheal instillation of a mixed suspension of budesonide 0.25 mg/kg and Curosurf 200 mg/kg/dose. Neonates were followed untill discharge for the primary outcome which was BPD and secondary outcomes including sepsis, patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC). ***Results:*** The mean gestational age and birth weight of the studied neonates were 28.3±1.6 weeks and 1072.0±180.0 g, respectively. The demographic characteristics and RDS score were similar in the two groups. BPD occurred in 24 (37.5%) neonates in the surfactant + budesonide group and 38 (59.4%) neonates in surfactant group, $p = 0.040$. Hospital stay was 29.7±19.2 days (median = 30 days) in the surfactant group and 23.3±18.1 days (median = 20 days) in the surfactant + budesonide group, $p = 0.050$. The rates of sepsis, PDA, ROP, and NEC were not significantly different in the two groups. ***Conclusions:*** 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 assessments are needed to confirm our findings before its routine use can be recommended.

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.[1]

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.[1–3] 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.[4,5] BPD risk factors include lower gestational age[6,7] and birth weight,[8,9] male gender,[10] white race and genetic factors,[11] perinatal asphyxia,[12] patent ductus arteriosus (PDA),[10,13] and mechanical ventilation parameters.[14–16]

Since there is marked variation among medical centers in BPD rates, it is suggested that specific care practices can modify BPD occurrence. There are preclinical and clinical studies that indicate the role of inflammatory reactions in the pathogenesis of RDS and BPD.[3,17] Researchers showed inflammatory mediator release in response to pulmonary toxins, including oxidants, free radicals, hypoxia, infection,

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or volutrauma. BPD appears to be induced by pro-inflammatory cytokines, chemokines, and proteinase-mediated events.[18–21] Corticosteroids as anti-inflammatory agents have been studied to prevent BPD. However, using systemic corticosteroids in the first month of life may increase the risk of long-term side effects in preterm infants.[22,23] Because of the adverse neurodevelopmental effects of systemic steroids, there is a tendency to research airway administration of steroids. Intratracheal instillation is a better way to administer corticosteroids with direct drug introduction into the alveolar space and the least systemic adverse effects. Budesonide is a corticosteroid with a local anti-inflammatory effect with 10-fold stronger potency[24] in reducing pro-inflammatory cytokine release, including tumor necrosis factor and interleukin-1β.[25] Budesonide has good absorption and persistence in the lungs because of budesonide ester formation at the carbon 21-hydroxyl group and slow free budesonide release.[26] 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 four trials of instillation of steroids) from 1993 to 2016 indicated that it is associated with a lower likelihood of BPD than placebo with no benefit concerning mortality.[27] BPD or mortality rate was significantly lower only in the group treated with budesonide. The duration, dose, type, and inhalation or instillation of steroids using surfactant as carrier were inconsistent across studies. The duration of inhalation of corticosteroids ranged from three 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.

METHODS

This randomized clinical trial was conducted in the neonatal intensive care unit (NICU) of Al Zahra Hospital, a tertiary university referral center in the North West of Iran. The study was approved by the ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.041) and registered in the Iranian Registry of Clinical Trials (IRCT 20100512003915N20). Parental informed written consent was obtained before patient enrollment. Considering the findings of Yeh et al,[28] in 2015 as a baseline and reducing the rate of BPD from 66% to 42% in the budesonide group with a power of 80% and 0.05 alpha we estimated that 64 cases were needed for each group. We estimated 67 neonates for each group considering potential drop-outs. Infants with major congenital anomalies, birth asphyxia (Apgar score < 4 at 5 minutes after birth), who had prolonged resuscitation, and lethal cardiopulmonary disorder were excluded.

Inborn preterm infants at < 30 weeks gestational age and with a birth weight < 1500 g who had RDS and needed surfactant replacement therapy from July 2018 to April 2019 were eligible for inclusion in the study. Gestational age was determined by first-trimester ultrasound examination and confirmed by neonatal examination using Ballard gestational age scoring.[29] At birth, all neonates received nasal continuous positive airway pressure (CPAP) 5–6 cm H_2O by infant T-piece resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) and transferred to the NICU covered with a plastic bag in portable incubators. In the NICU, 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_2O and flow 6–7 L/min. The diagnosis of RDS was based on clinical signs and symptoms and confirmed by radiologic findings. RDS severity was determined using RDS score. Surfactant was given to infants who met clinical and radiologic criteria for RDS as Intubation- SURfactant- Extubation treatment method within two to six hours of life. Targeted oxygen saturation (SPO_2) 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) 200 mg/kg/dose (2.5 mL/kg/dose) after premedication with fentanyl 1–2 mic/kg. Patients in the surfactant + budesonide group were 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 200 mg/kg/dose (2.5 mL/kg/dose). An independent nurse prepared syringes with surfactant and surfactant

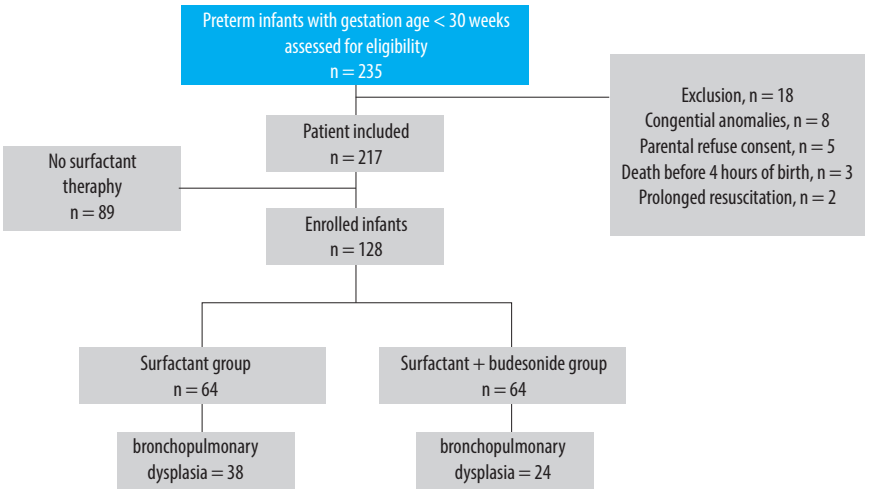

Figure 1: Flow chart of inclusion.

+ 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 two hours of life in both groups. Surfactant administered as RDS rescue treatment to infants receiving CPAP at a pressure > 5 cm H_2O who needed a fraction of inspired oxygen (FiO_2) of > 30% to maintain SPO_2 between 88% and 92%. Following surfactant administration, when the spontaneous respirations resumed, and after adequate heart rate and SPO_2 establishment, the endotracheal tube was removed, and the infants were weaned to nasal CPAP. Endotracheal intubation was reserved for infants with severe respiratory distress, apnea or ineffective respiratory effort, or hemodynamic instability. The second dose of surfactant was administered to infants with persistently increased breathing and FiO_2 requirements of > 30%, while other problems were excluded.

CPAP was weaned in increments of 1 cm H_2O every 12–24 hours when infants were stable by considering 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 3–4 L/min delivered by binasal prongs. We considered CPAP failure when the extubated infant developed respiratory distress and needed a FiO_2 > 0.4 for maintaining SPO_2 > 90%. Arterial blood gas parameters were recorded at admission and six hours intervals after surfactant administration. The neonatologist who managed the neonates was blinded to the patients' group. After 28 days of birth, another independent researcher (also blinded to the patients' groups) measured the patient's oxygen dependency. Infants who had continued to receive oxygen were considered as having BPD. For all enrolled neonates, a detailed questionnaire was completed.

Premature rupture of membranes refers to a rupture of membranes before 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/$mm^{3)}$, tachycardia (> 100 bpm), fetal tachycardia (> 160 bpm), uterine tenderness, and stained or unusual 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 five to seven of birth to diagnose intraventricular hemorrhage (IVH) by an experienced pediatric radiologist. PDA was diagnosed based on clinical signs and confirmed by echocardiography performed by an expert pediatric cardiologist.

The primary outcome was BPD. BPD was defined as the need for supplemental oxygen for at least 28 days and its severity was determined at 36 weeks based on the fraction of inspired oxygen.[30]

The secondary outcome included the total days of hospital stay and other complications of prematurity, including sepsis, necrotizing enterocolitis (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 the

presence of clinical signs and symptoms but negative blood culture.

After pupillary dilation, the retinas were examined through an indirect ophthalmoscope. ROP was classified according to the international classification.

The statistical analyses were performed using SPSS (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Quantitative data were presented as mean±standard deviation 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 < 0.050 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 [Figure 1]. Seventy-eight neonates (60.9%) were boys. The mean gestational age and birth weight of studied neonates were 28.3±1.6 weeks and 1072.0±180.0 g, respectively. The most common maternal risk factor for preterm labor was preeclampsia in 35 (27.3%) cases. There were no cases of chorioamnionitis.

The demographic characteristics were similar in the two groups [Table 1].

Mechanical ventilation was needed in 28 (43.8%) neonates in the surfactant group and 24 (37.5%) neonates in the surfactant + budesonide group, $p = 0.620$. The maximum respiratory support types and the mean duration of each are presented in Table 2. The mean duration of respiratory support was significantly longer in the surfactant group in comparison with surfactant + budesonide group (mechanical ventilation 2.8±0.6 vs. 0.8±0.1 days, $p = 0.006$, nasal CPAP 5.2±3.0 vs. 4.0±3.5 days, $p = 0.040$, 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; 38 (59.4%) neonates were in surfactant group and 24 (37.5%) neonates were in the surfactant + budesonide group, $p = 0.040$. The severity of BPD was mild in 27 (71.0%), moderate in 9 (23.7%), and severe in 2 (5.3%) neonates in the surfactant group vs. mild in 20 (83.3%) and moderate in 4 (16.7%) neonates in surfactant + budesonide group.

Table 1: Demographic characteristics of preterm infants in the two groups.

Characteristics	Surfactant group n = 64	Surfactant + budesonide group n = 64	*p*-value
Gender			
Male, n (%)	40 (62.5)	38 (59.4)	0.850
Gestational age, weeks	28.4 ± 1.5	28.2 ± 1.7	0.380
Birth weight, g	1089.0 ± 1680	1055.0 ± 192.0	0.270
Cesarean delivery, n (%)	53 (82.8)	52 (81.3)	1.000
Maternal preeclampsia, n (%)	21 (32.8)	14 (21.9)	0.210
PROM, n (%)	16 (25.0)	12 (18.8)	0.520
Placental abruption, n (%)	4 (6.3)	6 (9.4)	0.510
Maternal diabetes mellitus, n (%)	1 (1.6)	2 (3.1)	0.510
Maternal hypothyroidism, n (%)	6 (9.4)	8 (12.5)	0.570
Multiple gestations, n (%)	26 (40.6)	18 (28.1)	0.130
Maternal age, years	28.2 ± 6.7	29.7 ± 5.7	0.180
Antenatal corticosteroids, n (%)	55 (85.9)	49 (76.6)	0.640
RDS score, median 7	6.5 ± 0.9	6.6 ± 0.9	0.780
Apgar score			
1 min	6.1 ± 1.7 (median = 6)	5.9 ± 1.7 (median = 6)	0.590
5 min	7.8 ± 1.4 (median = 8)	7.6 ± 1.9 (median = 8)	0.600

PROM: premature rupture of membrane; RDS: respiratory distress syndrome.

Repeated doses of surfactant replacement therapy were used in 34 (26.6%) of studied neonates: 24 (37.5%) were in the surfactant group and 10 (15.6%) in the surfactant + budesonide group, $p = 0.010$. The observed complications of prematurity are presented in Table 3.

Vitamin A was used in 59 (92.2%) neonates in both groups for BPD prevention in the first four weeks of life. Caffeine was used in all neonates in both groups. Neonates received systemic steroids as acceleration of extubation or BPD management.

We had no cases of gastrointestinal bleeding, intestinal perforation, and hypertrophic cardiomyopathy in our studied neonates. We did not assess growth failure in our neonates after discharge.

Table 2: Respiratory support in two groups.

Varaibles	Surfactant group n = 64	Surfactant + budesonide group n = 64	*p*-value
MV, n (%)	28 (43.8)	24 (37.5)	0.620
NCPAP, n (%)	61 (95.3)	59 (92.2)	0.470
HFNC, n (%)	54 (84.4)	52 (81.3)	0.460
Duration of MV, days	2.8 ± 0.6	0.8 ± 0.1	0.006
Duration of CPAP, days	5.21 ± 3.0	4.0 ± 3.5	0.040
Duration of HFNC, days	7.7 ± 0.9	4.1 ± 0.5	0.001
The number of surfactant therapy			
1	40 (62.5)	54 (84.4)	0.010
2	20 (31.3)	9 (14.1)	
3	4 (6.3)	1 (1.6)	
FiO_2			
One hour after treatment	0.3 ± 0.1	0.3 ± 0.1	0.370
After 24 hours	0.3 ± 0.0	0.2 ± 0.0	0.010
PH			
Admission	7.2 ± 0.0	7.2 ± 0.0	0.850
Six hours after treatment	7.3 ± 0.0	7.3 ± 0.0	0.640
PCO_2			
Admission	50.7 ± 9.8	50.3 ± 13.7	0.870
Six hours after treatment	40.6 ± 8.5	38.0 ± 10.9	0.130
HCO_3			
Admission	20.0 ± 3.0	20.2 ± 3.3	0.630
Six hours after treatment	20.4 ± 2.3	19.8 ± 3.5	0.210

MV: mechanical ventilation; NCPAP: nasal continuous positive airway pressure; HFNC: high flow nasal cannula; FiO_2: fraction of inspired oxygen; PH: potential hydrogen; PCO_2: partial pressure of carbon dioxide; HCO_3: bicarbonate.

Table 3: Complications of prematurity in two groups.

Variables	Surfactant group n = 64	Surfactant + budesonide group n = 64	*p*-value
BPD, n (%)	38 (59.4)	24 (37.5)	0.040
Hospital stay, days	29.7 ± 19.2 (median = 30)	23.3 ± 18.1 (median = 20)	0.050
PDA, n (%)	17 (26.6)	13 (20.3)	0.200
Pneumothorax, n (%)	3 (4.7)	1 (1.6)	0.160
Pulmonary hemorrhage, n (%)	5 (7.8)	3 (4.7)	0.240
Sepsis, n (%)	25 (39.1)	21 (32.8)	0.230
ROP, n (%)	3 (4.7)	2 (3.1)	0.320
NEC, n (%)	4 (6.3)	2 (3.1)	0.200
Mortality, n (%)	9 (14.1)	6 (9.4)	0.290

BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis.

DISCUSSION

Intratracheal administration of surfactant + budesonide compared with solitary surfactant replacement therapy was associated with reduced BPD rate in preterm infants who had RDS. Patients treated with surfactant + budesonide required less frequently repeated doses of surfactant replacement therapy, less respiratory support, and shorter hospital stays. Similar to our findings, in a clinical trial conducted in the USA and Taiwan, 265 very low birth weight infants with severe RDS who required mechanical ventilation within the 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 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 the two groups, similar to our study. In contrast to our finding, they reported a significantly lower incidence of PDA without a significant difference in the duration of mechanical ventilation or oxygen therapy.[30] In another study, 116 very low birth weight infants with severe RDS that needed mechanical ventilation after birth were assessed. Early tracheal instillation of budesonide using surfactant as a vehicle resulted in lower mean airway pressure on days one and three, lower PCO_2 and oxygen index during the first three days, and lower death or chronic lung disease.[31]

The exact mechanism by which the intratracheal budesonide may reduce the incidence of BPD is unknown. Intratracheal instillation of budesonide and surfactant in rabbits could increase the alveolar area, decrease the alveolar wall thickness, and increase the density of lamellar bodies protein levels in type II epithelial cells of pulmonary alveoli.[32] It is suggested that surfactant act as a vehicle that facilitates the delivery of budesonide to the lung periphery, and enhance its solubility and absorption.[27] Intratracheal budesonide is associated with improved gas exchange, oxygenation index, reduced pulmonary edema, and inflammation.[25] Yeh et al,[33] in a pilot study showed that more than 80% of budesonide might remain in the lungs for up to eight hours after intratracheal instillation of surfactant (Survanta) and budesonide.[33] They estimate that 5–10% of budesonide may remain in the lungs by one week.[33] These effects account for diminished rate, duration of respiratory support,

and mechanical ventilation-induced lung injuries. The FiO_2 24 hours after treatment and the need for repeated doses of surfactant replacement therapy was significantly lower in the surfactant and budesonide group in our study.

Since the blood gas analyses after surfactant administration were not significantly different among the two studied groups, we suggest our used volume of budesonide could not 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 preventing BPD using a budesonide and surfactant combination. We have not assessed the long-term possible side effects of surfactant + budesonide replacement therapy in preterm infants. Our study was limited by its small sample size, short-term follow-up, and lack of long-term neurodevelopmental assessment. We recommend future studies with large number of patients and long-term follow-up to determine possible side effects.

CONCLUSION

The intratracheal administration of surfactant and budesonide combination improves short-term outcomes in preterm infants with respect to the incidence of BPD, need for repeated doses of surfactant, and the 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.

Disclosure

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