ORIGINAL ARTICLE

The efficacy of intratracheal administration of surfactant and budesonide combination in the prevention of bronchopulmonary dysplasia

Manizheh Mostafa Gharehbaghi[1], Majid Mhallei[2], Shalale Ganji[3], Sanaz Yasrebinia[3]

[1]Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, [2]Department of Pediatrics and Neonatology, Children Hospital, Tabriz University of Medical Sciences, Tabriz, Iran, [3]Department of Pediatrics and Neonatology, Alzahra Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

Background: Bronchopulmonary dysplasia (BPD) remains a major problem in preterm infants that occurs in up to 50% of preterm infants. The inflammation plays an important role in its pathogenesis. This study was conducted to evaluate the efficacy intratracheal budesonide administration in combination with surfactant in the prevention of BPD in preterm infants. **Materials and Methods:** In a randomized controlled clinical trial, 128 preterm infants with gestation age <30 weeks and birth weight <1250 g who had respiratory distress syndrome (RDS) and need surfactant replacement therapy were studied. They randomly allocated into two groups, surfactant group (n = 64) and surfactant + budesonide group (n = 64). Patients were followed till discharge for the primary outcome which was BPD. **Results:** The mean gestation age and birth weight of studied neonates were 28.3 ± 1.6 weeks and 1072 ± 180 g, respectively. BPD was occurred in 20 (31.3%) neonates in surfactant + budesonide group and 38 (59.4%) patients in surfactant group, P = 0.02. Respiratory support was needed in two groups similarly, but 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). **Conclusion:** Based on our findings, the use of budesonide in addition to surfactant for rescue therapy of RDS significantly decreases the incidence of BPD and duration of respiratory support. Future studies are recommended with a large number of patients before routine administration of surfactant and budesonide combination.

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

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INTRODUCTION

Respiratory distress syndrome (RDS) is caused by a deficiency of pulmonary surfactant which is necessary to reduce surface tension at alveoli. After birth, increased surface tension if untreated causes progressive airway collapse.

The benefits of maternal antenatal corticosteroids in lung maturity had been reported in previous studies. The 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 born at <28-week gestational age.[4,5] BPD risk factors include lower gestation age[6,7] and birth weight,[8,9] male gender,[10] white race and genetic factors,[11] perinatal asphyxia,[12] patent ductus arteriosus,[10,13] and mechanical ventilation parameters.[14-16]

There are preclinical and clinical studies that suggest the role of inflammatory reactions in pathophysiology

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Address for correspondence: Dr. Manizheh Mostafa Gharehbaghi, Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail: gharehbaghimm@yahoo.com
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of RDS and BPD.[3,17] The importance of inflammation in pathogenesis of BPD was reported. Researchers showed inflammatory mediator release in response to pulmonary toxins including oxidants, free radicals, hypoxia, infection, or volutrauma.[18-21] Corticosteroids as anti-inflammatory agents have been studied to prevent BPD. Postnatal systemic corticosteroids may increase the risk of long-term side effects in preterm infants.[22,23] Because of adverse neuro-developmental effects of systemic steroids, there is a tendency to research inhaled 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[24] in reducing pro-inflammatory cytokine release.[25] It has well absorption and persistence in lungs because of budesonide ester formation at the carbon 21–hydroxyl group and slow free budesonide release.[26] Hence, budesonide is superior to other corticosteroids for intratracheal administration. This study was conducted to evaluate the efficacy intratracheal budesonide administration in combination with surfactant in the prevention of BPD in preterm infants.

MATERIALS AND METHODS

This randomized controlled clinical trial was conducted from October 2017 to June 2018 in a tertiary neonatal intensive care unit in North West of Iran. Inborn preterm infants with gestation age <30 weeks and birth weight <1250 g who had RDS with FiO_2 requirements more than 40% and need surfactant replacement therapy were eligible. Infants were excluded for major congenital anomalies, birth asphyxia (Apgar score <4 at 5 min after birth), and lethal cardiopulmonary disorder.

By using G power soft ware (Apponic Heinrich-Heine-University, Germany) 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. Two hundred and thirty-five preterm infants with gestation age <30 weeks were assessed for eligibility. Eighteen neonates were excluded because of congenital malformations, parental refuse, and low Apgar score. Two hundred and seventeen infants were met the inclusion criteria that 92 neonates did not need surfactant replacement therapy and remaining 128 neonates enrolled in the study. The study was approved by Ethic committee of Tabriz University of Medical Sciences by code IR.TBZMED.REC.1397.041 and was registered in Iranian Registry of Clinical Trials (IRCT) by number IRCT 20100512003915N20. Parental informed written consent was obtained before patient enrollment. Enrolled patients were randomly allocated in two groups by the block randomizationm.

All spontaneously breathing neonates received nasal continuous positive airway pressure (CPAP) started immediately after birth. 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 positive end expiratory pressure 5–6 cm H_2O and flow 6–7 l/min (Fisher and Paykel Health Care limited, New Zealand). Endotracheal intubation was reserved for infants who had apnea, ineffective respiratory effort, severe respiratory distress, or cardiopulmonary instability. Neonates in surfactant group were 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 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 and Curosurf 200 mg/kg/dose mixed in a single syringe. Surfactant was administered in the first 2 h of life by bolus administration through endotracheal tube with a short period of ventilation by T-piece resuscitator to facilitate the drug distribution in both groups. Our center protocol is the extubation of infants to CPAP as soon as possible (INSURE technique [Intubation-SURfactanct-Extubation]) to reduce the rate and duration of mechanical ventilation. Mechanical ventilation is used in cases with extubation failure that are unresponsive to noninvasive ventilation modes. CPAP pressure can then be individualized depending on clinical condition, oxygenation, and perfusion. Infants who weaned of nasal CPAP with mild tachypnea were supported by heated humidified high flow nasal cannula 3–4 l/min delivered by binasal prongs. Arterial blood gas parameters were recorded at admission and 6 h after surfactant administration. For all neonates, questionnaires were completed by an NICU nurse who was unaware of the aim of the study and patients groups.

Cranial ultrasound examination was performed on days 5–7 of birth for the diagnosis of intraventricular hemorrhage (IVH) by an experienced pediatric sonographist. Patent ductus arteriosus (PDA) was diagnosed based on clinical signs and confirmed by echocardiography performed by an expert pediatric cardiologist. Sonographist and cardiologist were blind about patients groups. The primary outcome was 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).

Analyses were performed by a person who did not involve in the diagnosis and treatment of infants using SPSS. Inc, Chicago, USA. 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 $P < 0.05$ 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 infants (60.9%) were boys. The mean gestation age and birth weight of studied neonates were 28.3 ± 1.6 weeks and 1072 ± 180 g, respectively. The most common maternal risk factor for preterm labor was preeclampsia 35 cases (27%). The demographic characteristics were similar in the two groups [Table 1].

Mechanical ventilation was needed in 28 neonates (43.7%) in surfactant group and 24 neonates (37.5%) in surfactant + budesonide group, $P = 0.63$. The types of used respiratory support devices and the mean duration of each of them are presented in Table 2. Five neonates (7.8%) in surfactant + budesonide group and 6 neonates (9.3%) in surfactant were not assessed for BPD because of death before 28 days after birth. BPD was detected in 58 (48.4%) neonates that 38 neonates (59.4%) were in surfactant group and 20 neonates (31.3%) in surfactant + budesonide group, $P = 0.02$. The severity of BPD was mild in 28 cases (73.6%), moderate 8 patients (28.5%), and severe in 2 neonates (7.1%) in surfactant group versus mild in 20 neonates (83.3%), moderate in 3 patients (12.5%), and severe in one neonate (4.1%) in surfactant + budesonide group.

Repeated doses of surfactant replacement therapy were used in 34 (26.5%) of studied neonates that 24 cases were in surfactant group and 10 neonates in surfactant + budesonide group, $P = 0.01$. The observed complications of prematurity are presented in Table 3 and Consort Diagram 1.

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 the United States and Taiwan, 265 very low birth weight infants with severe RDS and mechanical ventilation 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 was 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.[27] In another study, 116 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 on day 1 and 3, lower PCO_2 and oxygen index during first 3 days, lower death or chronic lung disease.[28]

The exact mechanism by which the intratracheal budesonide may reduce the incidence of BPD is unknown. Li *et al*. reported

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

	Surfactant group (*n*=64)	Surfactant+budesonide group (*n*=64)	*P*
Gender, male, *n* (%)	40 (62.5)	38 (59.3)	0.85
Gestation age, weeks	28.4±1.5	28.2±1.7	0.38
Birth weight, g	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
Decolman, *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, years	28.2±6.7	29.7±5.7	0.18
Apgar score			
1 min	6.1±1.7	5.9±1.7	0.59
5 min	7.8±1.4	7.6±1.9	0.60
Antenatal corticosteroids, *n* (%)	55 (85.9)	49 (76.5)	0.64

PROM=Premature rupture of membranes

Table 2: Respiratory support in two groups

	Surfactant group (*n*=64)	Surfactant+budesonide group (*n*=64)	*P*
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, days	2.8±0.6	0.8±0.1	0.006
Duration of CPAP, days	5.21±3.0	4.0±3.5	0.04
Duration of HFNC, days	7.7±0.9	4.1±0.5	0.001
The number of surfactant therapy			
1	40 (62.5)	54 (84.3)	0.01
2	20 (31.2)	9 (14)	
3	4 (6.2)	1 (1.5)	
Fio_2			
Admission	0.37±0.14	0.35±0.14	0.37
6 h after treatment	0.30±0.08	0.26±0.07	0.01
PH			
Admission	7.21±0.07	7.21±0.09	0.85
6 h after treatment	7.31±0.07	7.32±0.09	0.64
PCO_2			
Admission	50.7±9.8	50.3±13.7	0.87
6 h after treatment	40.6±8.5	38.0±10.9	0.13
HCO_3			
Admission	20.0±3.07	20.2±3.35	0.63
6 h after treatment	20.4±2.38	19.8±3.56	0.21

MV=Mechanical ventilation; NCPAP=Nasal continuous positive airway pressure; HFNC=High flow nasal cannula; PCO_2=Carbon dioxide pressure; HCO_3=Bicarbonate; CPAP=Continuous positive airway pressure

Table 3: Complications of prematurity in two groups

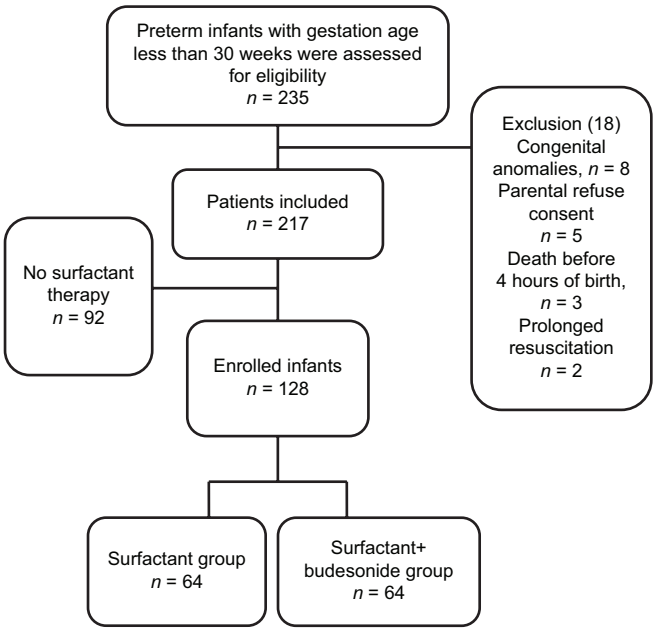
	Surfactant group (*n*=64)	Surfactant+budesonide group (*n*=64)	*P*
BPD, *n* (%)	38 (59.4)	20 (31.3)	0.02
Hospital stay	29.7±19.2	23.3±18.1	0.04
PDA, *n* (%)	17 (26.5)	13 (20.3)	0.53
Pneumothorax, *n* (%)	3 (4.6)	1 (1.5)	0.61
Pulmonary hemorrhage, *n* (%)	5 (7.8)	3 (4.6)	0.47
Sepsis, *n* (%)	25 (39)	21 (32.8)	0.58
ROP, *n* (%)	3 (4.6)	2 (3.1)	0.63
NEC, *n* (%)	4 (4.6)	2 (3.1)	0.40
Mortality, *n* (%)	9 (14)	6 (9.3)	0.58

BPD=Bronchopulmonary dysplasia; PDA=Patent ductus arteriosus; ROP=Retinopathy of prematurity; NEC=Necrotizing enterocolitis

that intratracheal 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.[29] It is suggested that surfactant acts as a vehicle that facilitate the delivery of budesonide to the lung periphery, enhance its solubility and absorption.[27] It is showed that intratracheal budesonide is associated with improved gas exchange, oxygenation index, reduced pulmonary edema, and inflammation.[25] Yeh *et al*. showed remaining budesonide in the lungs for up to 8 h after intratracheal administration[30] 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 h after treatment and the need for repeated doses of surfactant replacement therapy were significantly lower insurfactant + budesonide group in our study. The limitation of our study was the number of studied patients and it was done in a single tertiary center. The patients were followed till discharge in this study.

Since the early postsurfactant administration blood gas analyses were not significantly different among 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 prevention of BPD by budesonide + surfactant combination. We have not assessed the long-term possible side effects of budesonide + surfactant replacement



Consort Diagram 1: Consort diagram of inclusion

therapy in preterm infants. It is recommended future multicenter studies with large number of patients and their long-term follow up to determine possible side effects.

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.

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Conflicts of interest

There are no conflicts of interest.

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