Original Article

Budesonide and Surfactant Combination for Treatment of Respiratory Distress Syndrome in Preterm Neonates and Evaluation Outcomes

Fatemeh Baghal Safa[1], Mahmood Noorishadkam[1], Mohamad Hosein Lookzadeh[1], Seyed Reza Mirjalili[1], Sedigheh Ekraminasab[1,2]

[1]Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [2]Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Submitted: 08-Jun-2023
Revised: 04-Aug-2023
Accepted: 06-Aug-2023
Published: 21-Dec-2023

ABSTRACT

Background: Pulmonary inflammation plays a critical role in the pathogenesis of respiratory distress syndrome. The aim of this study was to compare the effectiveness of intratracheal administration combination of pulmonary surfactant (PS) and budesonide with surfactant alone in preterm neonates. **Materials and Methods:** This randomized clinical trial was performed in Yazd between 2020 and 2022. A total of 70 preterm neonates weighing between 800 and 1500 g were included in the study. **Results:** The risk of bronchopulmonary dysplasia (BPD) in infants treated with PS and budesonide was seven times lower than in the surfactant group alone ($P = 0.004$). Furthermore, in the intervention group, the hospitalization period ($P = 0.004$) and retinopathy of prematurity ($P = 0.02$) were significantly reduced. **Conclusion:** In these neonates, intratracheal administration of surfactant/budesonide combination significantly decreases the incidence of frequent apnea, BPD, continuous positive airway pressure therapy, and earlier discharge. There is a need for larger trials and an exact evaluation of side effects.

KEYWORDS: *Apnea, bronchopulmonary dysplasia, budesonide, newborn, pulmonary surfactants, respiratory distress syndrome*

INTRODUCTION

Respiratory distress syndrome (RDS) is a frequent respiratory disorder of premature newborns, principally demonstrated as dyspnea, granting, and other symptoms.[1] RDS is induced by a lack of surfactant secretion due to immaturity of type II pneumocytes in the alveoli.[2] If the increased surface tension is not treated, it may cause progressive airway collapse and respiratory distress due to ventilation mismatch.[3] RDS can be prevented with several lines of therapy, including prenatal steroids for mothers, exogenous surfactant, and ventilation for preterm newborns.[2,4] Mechanical ventilation is the traditional treatment for neonatal RDS (NRDS), which easily causes bronchopulmonary dysplasia (BPD) and other problems.[1] BPD is determined by alveolar simplification, abnormal pulmonary function, impaired vascular development, and arrest in lung growth.[5] Numerous investigations have shown that the inflammatory process is the main factor of pathogenesis in BPD and NRDS.[6] The NRDS is caused by an inflammatory process in the immature lung. Surfactant inactivation is caused by the leakage of serum proteins due to the severity of the inflammatory damage of the alveoli.[5,6] Anti-inflammatory agents like corticosteroids have a beneficial role in the management of NRDS by interfering with the inflammatory processes in the neonatal lungs[7,8] However, systemic corticosteroids can have multiple adverse effects, including intestinal bleeding and growth failure[9-11] Budesonide is a synthetic steroid from the glucocorticoid family with high local anti-inflammatory activity.[12] Due to its structure, budesonide has good absorption and retention in the lungs, therefore, it is perfect for intratracheal administration.[3]

Numerous clinical trials and meta-analyze study assessed the efficiency of corticosteroids (inhaled or

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jocn

DOI: 10.4103/jcn.jcn_52_23

Address for correspondence: Dr. Mahmood Noorishadkam, Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
E-mail: noorishadkam@ssu.ac.ir

How to cite this article: Safa FB, Noorishadkam M, Lookzadeh MH, Mirjalili SR, Ekraminasab S. Budesonide and surfactant combination for treatment of respiratory distress syndrome in preterm neonates and evaluation outcomes. J Clin Neonatol 2023;12:135-41.

intracheal) on treatment of RDS and prevention of BPD in preterm and very preterm infants and also in very low birth weight (VLBW) infants. Venkataraman *et al*. in 2016 in a systematic review and meta-analysis, evaluated the efficacy of intratracheal injection of surfactant/budesonide combination in preventing BPD in VLBW infants. They concluded this combination was associated with a reduced incidence of BPD in VLBW infants.[11] Since several studies have shown the administration of corticosteroids is still considered an open research area, especially in side effects and mortality rate, we did this randomized clinical trial study to assess the effectiveness of combining intratracheal budesonide with surfactant in treating RDS and preventing BPD in premature infants. Also, we wanted to evaluate the adverse effect of budesonide/surfactant in these neonates.

Materials and Methods

In a single-blind randomized clinical trial between December 2020 and January 2022, all infants with RDS were evaluated shortly after birth for study eligibility at three tertiary centers: In neonatal intensive care unit (NICU) of Shahid Sadoughi hospital in Yazd. Inclusion criteria were defined within 2 h after birth and included (1) birth weight between 800 and 1500 g, (2) who were diagnosed as moderate to severe RDS (3) mechanical ventilation, (4) absence of severe congenital anomalies, lethal cardiopulmonary disorder, sepsis and asphyxia.

Scorning of respiratory distress syndrome

According to Downe's score of standard treatment guidelines of RDS in the newborn, we considered a RDS score of 5–7 as moderate and a score >7 as severe RDS.[13]

Study patients

A total of 70 premature infants with RDS (respiratory score more than 6) occurring within 2 h of birth and birth weight between 800 and 1500 gr were selected as the subjects. The infants in control group underwent PS, and those in intervention group underwent budesonide combined with PS.

In order to determine the sample size according to the similar studies conducted on the percentage of surfactant alone and surfactant and budesonide 35 in the other group and the confidence level is 95% and the power of the test is 80%, the exact sample size was calculated using PASS 11 software in each group. This trial was approved by the Research Ethics Board of Shahid Sadougi University of Medical Sciences. Consent was obtained from the parents of all infants.

Randomization

All neonates were randomly divided into two intervention and control groups with 35 cases in each group. In the intervention group, there were 19 females and 16 males with an average gestational age of 29.94 ± 2.11 weeks and an average body weight of 1.186 ± 0.224 kg. In the control group, there were 17 females and 18 males, with an average gestational age of 29.34 ± 2.19 and an average body weight of 1.139 ± 0.230 kg. There was no significant difference in gestational age, gender, and body weight between the two groups, and the overall data were comparable.

Research methods

Two groups of infants were treated as usual and warm maintenance was performed after hospitalization. In addition, electrocardiogram monitoring, blood gas monitoring, and intravenous feeding were performed for the patient. The airway was cleaned before administration. Medicines are injected into the lungs through the trachea within 4 h after birth and can be injected again 6–12 h after birth if necessary. If needed, a ventilator can be used to support breathing. The ventilator parameters were adjusted according to the patient's condition and blood gas analysis and after the patient's physical symptoms returned to normal, the tube was removed.

If, after 8 h, the baby is still under ventilation with a ventilator or needs 35% oxygen with FiO2 more than 40% and mean airway pressure more than 7, the next dose of surfactant was injected alone. All infants in this study were followed up until the end of the hospitalization period, and the primary and secondary outcomes were examined.

Drug administration

Control group

They received only surfactant in the amount of 2.5cc/kg of curosurf solution (3cc/240 mg curosurf) (manufactured by Chiesi, Italy) by intratracheal method.

Experimental group

They were given a mixture of surfactant and budesonide. They received the same amount of surfactant and also received budesonide 250 μ/kg of palmicort from a vial of 0.25 mg/ml (manufactured by AstraZeneca, Sodertalje, Sweden) by intratracheal method. Coded intratracheal packages containing drugs were delivered to our center to ensure random concealment. Neonates were randomized at the time of signing the first prescription for the study drug.

Outcome measurements

We followed up these neonates for 60 days. Then they were evaluated for primary and secondary outcomes.

All variables were acquired from the pregnancy card, mother's history, and NICU records that entered in the information sheet. Daily follow-ups including vital signs and daily oxygen saturation were observed or obtained from nursing charts. The primary outcome includes the frequency of pneumothorax, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), apnea episode, and sepsis. The secondary outcomes include incidence of retinopathy of prematurity (ROP), BPD, mortality, hospitalization duration, need to re-intubation a tracheal tube, need for surfactant injection, the average duration of need for CPAP, need for high-flow nasal cannula (HFNC), and the average duration of need for mechanical ventilation.

Statistical analysis

Data were presented as mean and standard deviation. Normally distributed quantitative variables were compared by student's *t*-test. The independent-samples *t*-test was used to compare the two groups. Paired-samples *t*-test was used for comparisons in the same group. For qualitative data, the Chi-squared test was used. The results of intergroup comparison were $P < 0.05$, which indicated that the differences were statistically significant. Fisher's exact test was also used to compare the frequency of qualitative variables. The outcomes were investigated by multivariate logistic regression. All statistical analyses were performed performed using IBM SPSS software version 21 (Chicago, IL, USA).

Results

The demographic characteristics and respiratory score of the two groups are shown in Table 1. Finally, 70 neonates were included in this study, 35 neonates for mixed surfactant and budesonide group and 35 neonates for just surfactant for control group. The mean of gestational age in the PS group and budesonide/PS was 29.34 ± 2.19 and 29.94 ± 2.11, respectively [Table 1].

Frequency of apnea and severity of intraventricular hemorrhage

According to Fisher's exact test, the frequency of apnea in two groups was statistically significant $P = 0.03$. The occurrence of apnea in high frequency in the Corosurf group alone is equivalent of three patients (8.6%), but in the Corosurf/Palmicort group, apnea did not occur more than four times; on the other hand, almost two groups are less frequently in terms of frequency of apnea episodes were equal. The frequency of IVH according to Fisher's exact test in two groups was similar ($P = 0.75$) [Table 2].

Reintubation of tracheal tube and the frequency of surfactant injection

According to Fisher's exact test, the two groups did not have a statistically significant difference in the frequency of needing to reintubation the tracheal tube ($P = 0.10$), although in the intervention group, the frequency of endotracheal tube placement is clearly less. The frequency of surfactant injections in the surfactant alone group is more than in the surfactant + budesonide group. However, according to Fisher's exact test, there was no statistically significant difference between the two groups ($P = 0.14$) [Table 2].

Duration of the need for respiratory support

According to the Mann–Whitney *U*-test, there was no statistically significant difference in the average duration of ventilation and HFNC in the two studied groups. The average duration of CPAP in the group treated with surfactant + budesonide was 7.77 ± 6.30 days and less than the group treated with surfactant alone, which was 13.9 ± 12.0, which is a statistically significant difference ($P = 0.02$).

Average time of starting feeding and reaching full feed

According to Fisher's exact test, feeding started earlier in the intervention group, but this difference is not significant. Based on the Chi-squared test,

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

Characteristics	Surfactant group (*n*=35)	Surfactant + budesonide group (*n*=35)	*P*
Gender, *n* (%)			
Male	18 (51.4)	16 (45.7)	0.63
Female	17 (48.5)	19 (54.2)	0.63
Gestational age (weeks)	29.34±2.19	29.94±2.11	0.25
Birth weight (g)	1139.86±230.28	1186±224.14	0.39
Mode of delivery, *n* (%)			
Normal vaginal delivery	5 (14.2)	7 (20)	0.56
Cesarean section	30 (85.7)	28 (80)	0.56
Apgar score 5 min	6.34±2.73 (MD=7)	7.43±2.18 (MD=8)	0.92
RDS score, first hour	6.94±1.08 (MD=7)	7.29±0.98 (MD=8)	0.18
RDS score, second hour	6.09±1.50 (MD=6)	6.26±1.22 (MD=6)	0.69

RDS - Respiratory distress syndrome; MD - Mean deviation

Table 2: Frequency of intraventricular hemorrhage, apnea, reintubation, and doses of surfactant in two groups

Variables	Surfactant group (*n*=35), *n* (%)	Surfactant + budesonide group (*n*=35), *n* (%)	*P*
IVH			
Grade 1	7 (20)	7 (20)	0.75
Grade 2	7 (20)	7 (20)	
Grade 3	2 (5.7)	4 (11.4)	
Grade 4	0	1 (2.9)	
Episode of apnea			
Episode 1	1 (2.9)	6 (17.1)	0.03
Episode 2	6 (17.1)	6 (17.1)	
Episode 3	5 (14.9)	1 (2.9)	
Episode ≥4	3 (8.6)	0	
The frequency of the need to reintubation a tracheal tube			
Did not need	22 (62.9)	23 (65.7)	0.01
Turn 1	6 (17.1)	9 (25.7)	
Turn 2	2 (5.7)	3 (8.6)	
Turn 3	49 (11.4)	0	
Turn ≥3	1 (2.9)	0	
Frequency of doses of surfactant repeat			
Turn 1	18 (51.4)	21 (60)	0.14
Turn 2	10 (28.6)	14 (40)	
Turn 3	6 (17.1)	0	
Turn 4	1 (2.9)	0	

IVH - Intraventricular hemorrhage

feeding is completed faster in the intervention group, but the two groups were not statistically significant (P = 0.23) [Table 3].

Side effects of treatment in the two study groups

Side effects of treatment with surfactant in two groups using the Chi-square test were checked and the two groups were similar in terms of occurrence of PDA, NEC, pneumothorax, and sepsis then there was no significant statistical difference. The rate of ROP requiring treatment in the group treated with surfactant + budesonide was 12 patients (34.3%) and in the group that received only surfactant, this rate was higher and equal to 22 patients (62.9%) and was statistically significant (P = 0.02). There was no statistically significant difference in the frequency of death in the two studied groups. According to the table, the prevalence of BPD and the duration of hospitalization were lower in the intervention group and the difference between the two groups was statistically significant [Table 4].

Primary outcome

According to logistic regression, the possibility of pneumothorax in the control group is 2.2 times higher than in the intervention group. Furthermore, IVH occurred 0.7 times more often in the group treated with Corosurf alone than in the group treated with Palmicort and Corosurf (in the intervention group, the odds of IVH were slightly higher). IVH occurred in the group treated with Corosurf alone 0.7 times more often than in the group treated with Pulmicort and Corosurf (in the intervention group, the chance of IVH occurrence was slightly higher). The probability of NEC in the control group is 2.5 times higher than in the intervention group. Furthermore, the chance of PDA in the control group is 2.4 times that of the intervention group. The occurrence of apnea more than once in the control group is 2.6 times higher than in the intervention group. The possibility of sepsis in the control group was 1.7 times higher than in the intervention group [Table 5].

Secondary outcomes

The probability of ROP in the control group is 3.2 times higher than in the intervention group. The probability of BPD in the control group is seven times higher than the intervention group. But the chance of death in the control group compared to the intervention group is 0.37 times, which means that more deaths occurred in the intervention group but it wasn't significant. The length of hospitalization for more than 1 month in the control group is 3.3 times compared of the intervention group.

Compared to the intervention group, the probability of reintubation more than 1 time in the control group is 2.6 times higher. But on the contrary, the need to receive surfactant ≥1 time in the intervention group

Table 3: Determining and comparing the duration of the need for respiratory support and the average time of starting feeding and reaching full feed 120 cc/kg in the two study groups

Variables (days)	Surfactant group (*n*=35)	Surfactant + budesonide group (*n*=35)	*P*
Ventilator	6.11±12.33 (MD=1)	3.60±5.40 (MD=2)	0.85
CPAP	13.90±12.00 (MD=10)	7.77±6.30 (MD=8)	0.02
HFNC	4.83±5.52 (MD=4)	3.80±4.23 (MD=2)	0.47
Feeding start time, *n* (%)			
≤5	2 (5.7)	3 (8.6)	0.47
5–10	9 (25.7)	13 (37.1)	
≥10	24 (68.6)	19 (54.3)	
Time to reach full feed, *n* (%)			
≤10	0	0	0.23
10–15	5 (14.3)	9 (25.7)	
≥15	30 (85.7)	26 (74.3)	

CPAP - Continuous positive airway pressure; MD - Mean deviation ; HFNC - High-flow nasal cannula

Table 4: Comparison of the frequency of side effects and mortality in the two study groups

Variables	Surfactant group (*n*=35), *n* (%)	Surfactant + budesonide group (*n*=35), *n* (%)	*P*
IVH grade 3	2 (5.7)	4 (11.4)	0.75
IVH grade 4	0	1 (2.9)	0.75
BPD	14 (40)	3 (8.6)	0.004
PDA	26 (74.3)	19 (54.3)	0.08
ROP	22 (62.9)	12 (34.3)	0.02
Pneumothorax	6 (17.1)	3 (8.6)	0.47
Sepsis	8 (22.9)	5 (14.3)	0.1
NEC	12 (65.7)	6 (17.1)	0.35
Duration of hospitalization, mean±SD (days)	42.23±21.66 (MD=33)	30.11±20.25 (MD=25)	0.004
Mortality	4 (11.4)	9 (25.4)	0.22

BPD - Bronchopulmonary dysplasia; PDA - Patent ductus arteriosus; ROP - Retinopathy of prematurity; NEC - Necrotizing enterocolitis; IVH - Intraventricular hemorrhage; SD - Standard deviation

Table 5: Statistical model of logistic regression of primary outcomes

Variables	OR	95% CI
Pneumothorax	2.20	0.5–9.63
IVH	0.70	0.27–1.81
NEC	2.52	0.82–7.74
PDA	2.43	0.88–6.66
Apnea episode	6.28	1.29–30.53
Sepsis	1.77	0.51–6.09

PDA - Patent ductus arteriosus; NEC - Necrotizing enterocolitis; OR - Odds ratio; CI - Confidence interval; IVH - Intraventricular hemorrhage

is 1.4 times compared to the control group. The need for ventilator ≥10 days occurred in the control group 2.2 times compared to the intervention group. The need for CPAP ≥10 days in the control group was 3.18 times higher than the intervention group, and this rate was 1.29 times for HFNC ≥10 days [Table 6].

Discussion

Conventional treatments for RDS such as traditional mechanical ventilation can easily damage the immature lungs of premature neonates and affect their brain development.[13,14] Several studies have evaluated Surfactant + budesonide in preterm infants and found it to have a beneficial effect on lung function. The therapeutic effect of budesonide in the treatment of RDST is still debated.[15,16] Despite the almost universal acceptance of mild mechanical ventilation, noninvasive respiratory support, and the use of surfactant, BPD is one of the most common respiratory complications in VLBW infants. Therefore, more studies are needed. In this study, we investigate the effectiveness of intratracheal injection of Surfactant + budesonide in premature infants with RDS.

In our work administration of intratracheal combination of surfactant and budesonide in comparison to surfactant is more effective in prevention of BPD. Also, duration of the need for CPAP in newborns treated with Surfactant + budesonide was shorter than the newborns in Surfactant Group. Apnea incidence in the Surfactant + budesonide group did not occur more than 4 times but in the Surfactant, group alone is equivalent there are 3 patients (P = 0.03). The frequency of IVH according to Fisher's exact test in two groups was similar (P = 0.75). The incidence of need for reintubation

Table 6: Statistical model of logistic regression of secondary outcomes

Variables	OR	95% CI
ROP	3.24	1.22–8.63
BPD	7.19	1.82–27.79
Mortality	0.37	0.10–1.35
Hospitalization duration ≥30 days	3.3	1.23–8.899
The need to re-intubation a tracheal tube ≥1 time	2.66	0.62–11.30
The need for surfactant injection ≥1 time	1.41	0.55–3.65
The need ventilator ≥10 days	2.20	0.50–9.63
The need for CPAP ≥10 days	3.18	1.13–8.93
The need for HFNC ≥10 days	1.29	0.31–5.27

BPD - Bronchopulmonary dysplasia; ROP - Retinopathy of prematurity; OR - Odds ratio; CI - Confidence interval; CPAP- Continuous positive airway pressure; HFNC- High-flow nasal cannula

of tracheal tube and administration of the higher dose of surfactant, the average duration of ventilation and HFNC between two groups were not statistically significant difference. The average duration of CPAP in the group treated with Surfactant + budesonide was significantly less than the group treated with Surfactant alone ($P = 0.02$).

Several studies assessed Surfactant + budesonide in preterm neonates and indicated have useful effect on lung function. A systematic review of 20 trials of inhaled corticosteroids from 1993 to 2016 found that they were associated with a lower incidence of BPD than placebo and no mortality benefit.[17] The most similar work with us is study of Gharehbaghi *et al*. in 2020. They showed that the use of surfactant/budesonide for treatment of RDS in preterm neonates significantly reduced the incidence of BPD and the duration of respiratory support.[3] Bassler *et al*. in 2015, observed that among those who received initial inhaled budesonide, the incidence of BPD was lower than among those who received placebo, but this benefit may have come at the cost of increased mortality.[18] Moschino *et al*. in a retrospective study (2017–2019) suggested that intratracheal surfactant/budesonide for severe RDS did not affect the incidence of BPD, or death compared to surfactant alone.[19] In a randomized controlled trial from 2016 to 2018, Elfarargy *et al*. evaluated the value of administering inhaled budesonide in cases of NRDS. They observed that inhaled budesonide was associated with improvement in clinical and laboratory parameters in NRDS.[2] Yeh *et al*. in 2015 found that in VLBW infants with severe RDS, intratracheal administration of budesonide/surfactant compared with surfactant alone significantly reduced the incidence of BPD or death without immediate adverse effects.[20] Kothe *et al*., in 2020 observed that budesonide was associated with reduced severity of BPD, premature discharge, reduced use of mechanical ventilation, and short-term outcomes. But the overall rate of BPD remained unchanged with the addition of budesonide.[15] Anderson *et al*. in 2021 evaluated effect of surfactant/budesonide combination on Long-term neurodevelopmental follow-up and monitored for systemic effects of budesonide. They found no difference in developmental outcomes at the corrected age of 4–6 months or 18–22 months.[16]

Several mechanisms contribute to the budesonide's effectiveness in improving respiratory function and preventing BPD, including: Budesonide action as a carrier, local anti-inflammatory glucocorticoid, increases the synthesis of PS and antioxidant and inhibits the synthesis of prostaglandins and leukotriene's.[1]

In our study, as in Basler's study, the mortality rate was increased, because Systemic glucocorticoids may increase risk of neonatal infection. Also, in our intervention group, among the nine patients who died, six patients were positive for covid-19, which may contribute to the increase in mortality, but there was no significant difference in mortality between the two groups. We hypothesized that in the context of the crisis of COVID-19, the administration of Budesonide should be done more cautiously because unlike adults, most infected infants are asymptomatic and infants with underlying conditions are at increased risk of severe COVID-19 related mortality.[21,22] Previous studies that evaluated the combination of budesonide with surfactant found no changes in neurodevelopment in survivors.[12,16] We assessed complication and primary and secondary outcome in our subjects. Apnea episode in the primary outcomes and BPD in secondary outcomes were statistically significant. The biggest limitation of our study was the lack of long-term follow-up data on neonates. Therefore, in future studies, in addition to a more detailed assessment of risk factors, long-term follow-up, and complications should be investigated.

Conclusion

In this study, we used budesonide/surfactant combination in the treatment of RDS and prevention of BPD in LBW premature infants. We evaluated the efficacy and side effects of treatments with budesonide/surfactant compare surfactant on RDS in premature neonates. This study showed that the addition of budesonide to surfactant in the treatment of RDS in preterm neonates can effectively improve respiratory and pulmonary function compared to the use of surfactant alone. The use of budesonide with intratracheal surfactant can be effective in reducing the need for mechanical ventilation and other respiratory support methods or the development of BPD. However, there are still some shortcomings in this study, such as

the fact that it coincided with the period of Covid-19 and the total number of samples was small. Although side effects were not significant in our study, further studies are needed in this field. More studies are needed to increase the effectiveness of the drug in respiratory support and reduce side effects.

Acknowledgments

We are very grateful to the NICU staff of Shahid Sadoughi who participated effectively in this project. We also appreciate the families of the infants who cooperated in this study and clinical follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Zhang C. Evaluation of the efficacy of budesonide combined with pulmonary surfactants on the neonatal respiratory distress syndrome by pulmonary ultrasonography. Sci Program 2021;2021:1-6.
2. Elfarargy MS, Al-Ashmawy GM, Abu-Risha SM, Khattab HA. Inhaled budesonide in neonatal respiratory distress syndrome of near-term neonates: A randomized, placebo-controlled trial. J Pediatr Pharmacol Ther 2022;27:38-44.
3. Gharehbaghi MM, Ganji S, Mahallei M. A randomized clinical trial of intratracheal administration of surfactant and budesonide combination in comparison to surfactant for prevention of bronchopulmonary dysplasia. Oman Med J 2021;36:e289.
4. Lanciotti L, Correani A, Pasqualini M, Antognoli L, Dell'Orto VG, Giorgetti C, *et al.* Respiratory distress syndrome in preterm infants of less than 32 weeks: What difference does giving 100 or 200 mg/kg of exogenous surfactant make? Pediatr Pulmonol 2022;57:2067-73.
5. Michael Z, Spyropoulos F, Ghanta S, Christou H. Bronchopulmonary dysplasia: An update of current pharmacologic therapies and new approaches. Clin Med Insights Pediatr 2018;12.
6. Cai H, Jiang L, Liu Y, Shen T, Yang Z, Wang S, *et al.* Development and verification of a risk prediction model for bronchopulmonary dysplasia in very low birth weight infants. Transl Pediatr 2021;10:2533-43.
7. Ma H, Yan W, Liu J. Diagnostic value of lung ultrasound for neonatal respiratory distress syndrome: A meta-analysis and systematic review. Med Ultrason 2020;22:325-33.
8. Li L, Dong L, Zhao D, Gao F, Yan J. Classical dendritic cells regulate acute lung inflammation and injury in mice with lipopolysaccharide induced acute respiratory distress syndrome. Int J Mol Med 2019;44:617-29.
9. Yang D, Yang Y, Zhao Y. Ibudilast, a phosphodiesterase-4 inhibitor, ameliorates acute respiratory distress syndrome in neonatal mice by alleviating inflammation and apoptosis. Med Sci Monit 2020;26:e922281.
10. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Late (≥7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2021;11:CD001145.
11. Venkataraman R, Kamaluddeen M, Hasan SU, Robertson HL, Lodha A. Intratracheal administration of budesonide-surfactant in prevention of bronchopulmonary dysplasia in very low birth weight infants: A systematic review and meta-analysis. Pediatr Pulmonol 2017;52:968-75.
12. O'Donnell S, O'Morain CA. Therapeutic benefits of budesonide in gastroenterology. Ther Adv Chronic Dis 2010;1:177-86.
13. Murki S, Umamaheswari B, Yengkhom R. Respiratory Distress in the Term Newborn. IAP Standard Treatment Guidelines Committee. 2022:13.
14. Sakonidou S, Dhaliwal J. The management of neonatal respiratory distress syndrome in preterm infants (European consensus guidelines – 2013 update). Arch Dis Child Educ Pract Ed 2015;100:257-9.
15. Kothe TB, Sadiq FH, Burleyson N, Williams HL, Anderson C, Hillman NH. Surfactant and budesonide for respiratory distress syndrome: An observational study. Pediatr Res 2020;87:940-5.
16. Anderson CD, Kothe TB, Josephsen JB, Sadiq FH, Burleyson N, Williams HL, *et al.* Budesonide mixed with surfactant did not affect neurodevelopmental outcomes at 6 or 18 months corrected age in observational cohorts. J Perinatol 2021;41:1681-9.
17. Zhang ZQ, Zhong Y, Huang XM, Du LZ. Airway administration of corticosteroids for prevention of bronchopulmonary dysplasia in premature infants: A meta-analysis with trial sequential analysis. BMC Pulm Med 2017;17:207.
18. Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V, *et al.* Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med 2015;373:1497-506.
19. Moschino L, Nardo D, Bonadies L, Stocchero M, Res G, Priante E, *et al.* Intra-tracheal surfactant/budesonide versus surfactant alone: Comparison of two consecutive cohorts of extremely preterm infants. Pediatr Pulmonol 2021;56:2114-24.
20. Yeh TF, Chen CM, Wu SY, Husan Z, Li TC, Hsieh WS, *et al.* Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. Am J Respir Crit Care Med 2016;193:86-95.
21. Golshan-Tafti M, Ekraminasab S, Bahrami R, Asadian F. Mortality rate in hospitalized pediatric patients with COVID-19 infection in Iran: A systematic review and meta-analysis. World J Peri Neonatol 2022;5:30-9.
22. Lookzadeh MH, Ekraminasab S, Baghalsafa F. Outcome of a neonate born to a mother with COVID-19: A case report of vertical transmission. World J Peri Neonatol 2022;4:124-9.