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# Comparison of the effect of surfactant with and without budesonide on the outcomes of respiratory distress syndrome (RDS) in premature infants: a randomized control trial

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## Abstract

**Background** Respiratory distress syndrome (RDS) is a common problem in premature infants, whose treatment with surfactant increases their survival. Surfactant does not reduce chronic complications such as chronic lung disease. Using budesonide with surfactant may reduce some of these complications. This study aimed to compare the effect of surfactant with and without budesonide on the outcomes of RDS in infants.

**Methods** This double-blind, randomised control trial was conducted from September 2023 to April 2024 in the neonatal intensive care unit of Afzalipour Hospital, Kerman, Iran, on premature infants with a gestational age of less than 32 weeks with RDS requiring surfactant. Infants were randomly assigned to two groups: surfactant alone and surfactant with budesonide (30 neonates in each group). Infants were examined daily by neonatologists and the data was recorded in the study checklist by a nurse; both were unaware of the grouping. Data analysis was done using SPSS software version 26.

**Results** The use of surfactant with budesonide significantly reduced the average duration of ventilation ( $P=0.029$ ) compared to surfactant alone. However, this treatment approach did not cause a significant difference in other outcomes, including the need for additional doses of surfactant, intraventricular hemorrhage, pneumothorax, BPD, PIE, sepsis, pulmonary and gastrointestinal bleeding, NEC, the need for inotropes, and mortality between the two groups ( $P>0.05$ ).

**Conclusion** The use of surfactant with budesonide can reduce the duration of ventilation, but has little effect on other outcomes of RDS. The long-term prognosis of this type of treatment should be followed up at the age of 2 years, and more studies are needed to clarify its effectiveness.

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**Keywords** Premature infants, Respiratory distress syndrome, Surfactants, Budesonide

## Introduction

Premature birth, defined as occurring before 37 weeks of pregnancy, is a leading cause of childhood mortality, accounting for 18% of all deaths in children under five and 35% of all neonatal deaths (infants less than 28 days old) [1, 2].

The incidence of RDS is inversely related to low gestational age and affects mostly premature infants. It occurs in 60–80% of infants less than 28 weeks of gestation, and 15–30% between 32 and 36 weeks [3]. Initial respiratory support in infants with RDS has changed dramatically over the past decades, from invasive to non-invasive support which showed that the use of nCPAP instead of invasive mechanical ventilation in preterm neonates was associated with a lower incidence of Bronchopulmonary dysplasia (BPD) [4].

RDS caused by the lack of pulmonary surfactant, which is necessary to reduce alveolar surface tension. Increased surface tension, if left untreated, may cause progressive airway collapse [5]. It has been found that the use of surfactant for the treatment of RDS reduces the mortality rate [6].

Anti-inflammatory compounds and corticosteroids such as budesonide can stimulate the secretion of surfactant, reduce bronchospasm, edema and fibrosis of the lung and reduce the response to cells and inflammatory mediators in the damaged lung [7, 8]. Due to the systemic complications of these compounds and the negative impact on the neurological development of premature infants, the use of this treatment is limited and it is better to use local steroid compounds in infants instead of using systemic steroids [9, 10]. The results of animal studies indicate that intratracheal administration of surfactant and corticosteroids improves lung function [11–14].

Administering budesonide along with surfactant helps to improve the respiratory condition of premature infants and reduces the need for respiratory support in these infants without adding the side effects of corticosteroids [15]. Several studies have been conducted comparing the effect of surfactant with and without budesonide on the outcomes of RDS in infants [9, 15–19].

The results of a meta-analysis showed that topical glucocorticoids have direct effects on lung diseases without systemic side effects. For example, using budesonide as a carrier by injecting a liquid mixture of pulmonary surfactant (PS) into the trachea can significantly improve lung function [19] and shorten the time of mechanical ventilation [16].

Treatment of RDS with surfactant increases the survival rate of preterm infants. However, it does not reduce chronic complications like BPD. The review results in

meta-analyses have shown that administering corticosteroids in the airway along with surfactant is still considered as a research issue with the possibility of further investigation [9, 20]. Therefore, this study aimed to compare the effect of surfactant with and without budesonide on the outcomes of RDS in infants.

The lack of research in this area can result in several detrimental outcomes, such as consistently high mortality rates and negative effects on premature infants, alongside substantial financial burdens on both families and healthcare systems with the use of the intervention. On the other hand, if proven safe, this can help reduce mortality and related complications in premature infants. Additionally, it can deepen our understanding of the mechanisms behind surfactant and budesonide, opening the door to innovative strategies for RDS treatment.

## Method

### Research design and participants

The present study was a double-blind randomized clinical trial. This study aimed to compare the effect of surfactant with and without budesonide on the outcomes of respiratory distress syndrome in infants admitted to the neonatal intensive care unit.

The research population was all premature infants with a gestational age  $\leq 32$  weeks who had symptoms of RDS and needed treatment with surfactant. These infants were admitted to the neonatal intensive care unit of Afzalipour Hospital in Kerman between September 2023 to April 2024.

According to the European consensus on the management of respiratory distress in infants, the reason for choosing infants  $\leq 32$  weeks for this treatment is that one of the most important complications of RDS is bronchopulmonary dysplasia, which occurs in 50% of extremely preterm and early preterm infants [21].

Severe asphyxia, major congenital anomalies, shock and cardiovascular instability, infants with severe intrauterine growth restriction, infants born to mothers with chorioamnionitis, and refusal of consent by parents/guardians, were considered as exclusion criteria.

The sample size in this study is based on the Pan et al. study [9], which reported the incidence of BPD as 6% in the PS + budesonide group and 40% in the PS group. With a 95% confidence level and 80% power, the sample size was calculated to be 27 infants in each group using G-POWER software.

### Data collection

The RANDOM ALLOCATION RULE was used for random allocation in infants who met the conditions

for entering the study. For this purpose, 60 infants were randomly placed on the cards that were assigned to two groups inside the lottery container. Each card was taken out of the container randomly and without replacement and was allocated to the qualified infants who entered the study. In this way, they were placed in two groups: surfactant alone and surfactant with budesonide (30 neonates in each group). Given that the study was double-blinded, the clinical caregivers, who were part of a two-person intervention team and not involved in the direct care of the infants, were responsible for injecting and pre-filling the medication into syringes according to the patient's code. Also, the outcome evaluator completed the checklist based on the patient's evaluation without knowing the medication received.

Surfactant administration was indicated for infants born at or before 32 weeks of gestation who required tracheal intubation for stabilization in the early hours after birth. It also applied to infants needing CPAP for persistent respiratory distress, defined by the need for positive end-expiratory pressure (PEEP) greater than 6 cm H<sub>2</sub>O within the first two hours, and those requiring an inspiratory oxygen concentration (FiO<sub>2</sub>) above 40% if their gestational age was  $\leq$  32 weeks. For infants born at or before 26 weeks, a FiO<sub>2</sub> greater than 30% was used as a criterion. Neonatal specialists made these decisions [17].

In the control group, Beraksurf (Beractant), a natural surfactant made from bovine lung extract and produced by Tekzsim, Iran, was injected intratracheally at an initial dose of 4 cc per kilogram (200 mg/kg). The surfactant was drawn into a sterile syringe using a sterile 18G needle. In the intervention group, in addition to Beraksurf, budesonide suspension (Pulmicort, Respules, Aster-Zeneka, Sweden) was injected into the trachea at a dose of 0.25 mg per kilogram. The budesonide suspension was drawn into a sterile syringe, and then mixed gently with the measured surfactant dose in a single syringe to ensure homogeneity. The INSURE (intubate, surfactant, extubate) method was used for surfactant administration in this study.

In infants who experienced respiratory distress after first dose of surfactant, had gasping respiration, or required high-concentration oxygen (FiO<sub>2</sub> >30%) within 12 h of receiving surfactant, subsequent doses were prescribed if other conditions, such as pulmonary hypertension and congenital heart diseases were ruled out [22].

All infants were visited every day by professors or specialist assistants who did not know about the grouping of infants, and were examined and followed up in terms of the need for inspiratory oxygen concentration, the presence of respiratory distress, clinical signs of patent ductus arteriosus (PDA), abdominal distention, symptoms of septicemia and other complications of prematurity until

discharge or at least 28 days after birth in terms of oxygen requirement.

Then, all the patients' information was recorded in the special study checklist by neonatal fellows who did not know about the grouping of infants and the type of primary treatment for RDS.

### Outcomes

The primary end point of the study was a composite adverse outcome included the following: pulmonary hemorrhage (based on clear bloody secretions from the tracheal tube that is not related to trauma caused by suction), intraventricular hemorrhage (proved by ultrasound of the brain by an experienced physician), proven septicemia (by blood culture or other fluid culture) including cerebrospinal fluid or urine, which must be sterile), air leak syndrome including pneumothorax (due to increased oxygen demand and simple chest x ray, duration of mechanical ventilation and hospitalization, the need for an additional dose of surfactants surfactant, The need for inotropic medicine, proven necrotizing enterocolitis, Time to reach full nutrition, the patency of the ductus arteriosus (according to tachycardia, heart murmur, pulse band and confirmation by echocardiography) were detected and recorded.

### The secondary outcomes

The secondary outcomes included: chronic lung disease (BPD) and duration of hospital stay. 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 [23].

A data registration form was prepared for each patient. In order to complete the necessary information in each form, the information extracted from the newborn file was used.

### Ethical considerations

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (code: IR.KMU.AH.REC.1402.156). Also, it was registered in the clinical trial system in 06/04/2024 (clinical trial ID: IRCT20211218053444N3).

### Statistical analysis

Data analysis was done using SPSS software version 26. Descriptive statistics indicators (prevalence, frequency percentage, mean and standard deviation) and Chi-square and U-Man-Whitney statistical tests were used for data analysis.

**Table 1** Comparison of characteristics of infants in two groups (surfactant with and without budesonide)

| Variable                   | Group                      |                |                               |                | P-value* |
|----------------------------|----------------------------|----------------|-------------------------------|----------------|----------|
|                            | Surfactant with budesonide |                | Surfactant without budesonide |                |          |
|                            | Mean                       | Standard error | Mean                          | Standard error |          |
| Gestational age            | 30.62                      | 0.21           | 30.50                         | 0.23           | 0.812    |
| Apgar 1                    | 7.03                       | 0.29           | 7.03                          | 0.26           | 0.904    |
| Apgar 5                    | 8.30                       | 0.25           | 8.23                          | 0.22           | 0.832    |
| Mother's age               | 30.43                      | 1.16           | 28.80                         | 1.03           | 0.269    |
| Birth weight (Median ± SE) | 1250.66                    | 30.66          | 1300.66                       | 36.06          | 0.175    |
| Gender                     | N                          | %              | N                             | %              | 0.438    |
| Female                     | 18                         | 60.0           | 14                            | 46.7           |          |
| Male                       | 12                         | 40.0           | 16                            | 53.3           |          |

\* U-Man-Whitney test \*\* significance at 0.05 level

**Table 2** Comparison of frequency of variables in two groups (surfactant with and without budesonide)

| Variable                            | Group                      |                |                               |                | P-value* |
|-------------------------------------|----------------------------|----------------|-------------------------------|----------------|----------|
|                                     | Surfactant with budesonide |                | Surfactant without budesonide |                |          |
|                                     | Average                    | Standard error | Average                       | Standard error |          |
| Duration of hospitalization (days)  | 23.53                      | 1.82           | 28.53                         | 2.24           | 0.065    |
| Duration of ventilation (days)      | 8.90                       | 1.42           | 12.76                         | 1.29           | 0.029**  |
| Time to reach full nutrition (days) | 17.31                      | 1.40           | 19.86                         | 1.46           | 0.123    |

**Table 3** Comparison of the frequency of variables in two groups (surfactant with and without budesonide)

| Variable                                             |         | Group                      |                               | P-value* |
|------------------------------------------------------|---------|----------------------------|-------------------------------|----------|
|                                                      |         | Surfactant with budesonide | Surfactant without budesonide |          |
|                                                      |         | Frequency of Yes (%)       |                               |          |
| The need for the second and third dose of surfactant |         | 2 (6.7)                    | 1 (10.0)                      | 0.640    |
| Intraventricular hemorrhage                          | Grade1  | 1 (3.3)                    | 2 (6.7)                       | 0.807    |
|                                                      | Grade 2 | 7 (16.7)                   | 5 (23.3)                      |          |
|                                                      | Grade 3 | 0(0)                       | 1 (3.3)                       |          |
| Pneumothorax                                         |         | 9 (30.0)                   | 9 (30.0)                      | 1        |
| BPD                                                  |         | 7 (24.1)                   | 14 (46.7)                     | 0.071    |
| PIE                                                  |         | 9 (30.0)                   | 15 (50.0)                     | 0.114    |
| Sepsis                                               |         | 15 (50.0)                  | 17 (56.7)                     | 0.605    |
| Pulmonary hemorrhage                                 |         | 8 (26.7)                   | 6 (20.0)                      | 0.542    |
| Gastrointestinal bleeding                            |         | 4 (13.3)                   | 9 (30.0)                      | 0.117    |
| NEC                                                  |         | 16 (53.3)                  | 17 (56.7)                     | 0.795    |
| Need for inotropes                                   |         | 19 (63.3)                  | 22 (73.3)                     | 0.405    |

\* Chi-square test

## Results

Of the 72 neonates initially enrolled, 12 were excluded from the study: 5 due to parental withdrawal of consent and 7 because they did not meet the inclusion criteria. Thus 60 neonates were finally included in the analysis and were divided into two groups, each consisting of 30 individuals. The demographic characteristics of the two groups of infants are summarized in Table 1. There was no significant difference between the two groups in this regard.

According to Table 2, the average duration of hospitalization, ventilation duration and time to reach full feeding of infants in the surfactant group were higher than the surfactant and budesonide group. However this difference was statistically significant only in the duration of ventilation ( $P=0.029$ ); This means that in the surfactant group compared to the surfactant and budesonide group, infants needed longer ventilation (Table 1).

According to Table 3, 6.7% of infants in the combined treatment group and 10% in the surfactant group needed the second and third doses of surfactant ( $P=0.640$ ). This means that the need for additional doses of surfactant was almost the same in the two groups. 73.3% of infants in both groups did not have intraventricular bleeding. The frequency of pneumothorax was the same in two groups (surfactant with and without budesonide) ( $P=1$ ). 24.1% of infants in the combined treatment group and 46.7% in the surfactant group had BPD ( $P=0.071$ ). Given a near-medium effect size (0.49), it can be concluded that that the observed group difference is not only statistically meaningful but also potentially impactful from a clinical perspective. Furthermore, The calculated risk ratio of 1.96 indicates that neonates in surfactant group were nearly twice as likely to develop BPD as those in the combined treatment group, while the odds ratio of 2.81 suggests that the odds of developing BPD were almost three times higher in the same comparison. These measures collectively point toward a significant and clinically relevant association between group status and BPD occurrence. 30% of infants in the combined treatment group and 50% in the surfactant group had PIE ( $P=0.114$ ). 50% of infants in the combined treatment group and 56.7% in the surfactant group had sepsis ( $P=0.605$ ). 26.7% of infants in the combined treatment group and 20% in the surfactant group had pulmonary hemorrhage ( $P=0.542$ ). 13.3% of infants in the combined treatment group and 30% in the surfactant group had gastrointestinal bleeding ( $P=0.117$ ). 53.3% of infants in the combined treatment group and 56.7% in the surfactant group had NEC ( $P=0.795$ ). 63.3% of infants in the combined treatment group and 73.3% in the surfactant group needed inotropes (Table 3). In this study, 23.3% of infants in the combined treatment group and 20% in the surfactant group

had mortality. The average gestational age of those who died was 29 weeks.

According to the literature, RDS has a higher prevalence among males than females. Gender-based comparisons were made in most comparisons, except that:

- In girls, the mean length of stay in the combined group ( $21.88 \pm 2.7$  days) was significantly shorter than in the other group ( $30.21 \pm 2.9$  days) ( $P = 0.043$ ).
- In girls, the mean length of ventilation in the combined group ( $8.16 \pm 1.7$  days) was significantly shorter than in the other group ( $13.86 \pm 2.0$  days) ( $P = 0.38$ ).

In boys, the frequency of pulmonary hemorrhage was significantly higher in the combination treatment group (4/12; 33.3%) than in the other group (0%) ( $P = 0.024$ ).

## Discussion & conclusion

This study was designed and implemented to compare the effect of surfactant with and without budesonide on the outcomes of RDS in infants with a gestational age of less than or equal to 32 weeks hospitalized in the neonatal intensive care unit.

The result of our study showed that infants in the surfactant-only group required longer ventilation than those in the surfactant with budesonide group. Several studies have shown the beneficial effect of the combination of surfactant and budesonide in terms of reducing complications such as intraventricular haemorrhage, bronchopulmonary dysplasia, length of hospitalisation, and mortality [5, 15, 19, 24, 25], highlighting its benefits together in managing premature infants.

Also this finding was consistent with the evidence presented in the studies of Yi et al. [19] and Qarabaghi et al. [15]. Probably, the synergistic effects of these two drugs on improving the respiratory function and increasing the gas exchange capacity in the lungs of premature infants have facilitated and accelerated the process of weaning from the ventilator. Therefore, the findings of this study suggested the beneficial role of the combination of surfactant and budesonide in the optimal management of RDS in premature infants.

On the other hand, the examination of other outcomes of RDS showed that there was no significant difference between the two treatment groups in terms of the frequency of intraventricular bleeding, pneumothorax, BPD, PIE, sepsis, pulmonary and gastrointestinal bleeding, NEC, need for inotropes, and mortality.

Also, in the study of Bakhal Safa et al. [24], the risk of bronchopulmonary dysplasia in the group treated with the combination of pulmonary surfactant and budesonide was seven times lower than in the surfactant alone group.

This finding was inconsistent with the reduction of BPD in the surfactant group with budesonide in our study.

The study of T. Brett Kothe et al. [5] and Moschino et al. [26], showed that the use of the combination of budesonide and surfactant did not cause a significant change in the incidence of BPD, but it significantly reduced the duration of mechanical ventilation, which is consistent with the results of our study. In the Heo et al. [27] study it was seen that the use of surfactant and budesonide is not effective in reducing the duration of mechanical ventilation, which is contrary to the present study. The discrepancy between our outcomes and those reported outcomes may be attributable to the inclusion of infants with lower gestational age and lower birth weight in their studies.

The findings from this study suggest that the combination of intratracheal budesonide with surfactant may offer additional benefits over surfactant alone in reducing inflammation and possibly lowering the incidence of BPD in preterm infants. If confirmed in larger, multicenter trials, this approach could contribute to future updates of neonatal care guidelines and support the adoption of surfactant-budesonide therapy as part of routine clinical practice, particularly for infants at risk of BPD.

Considering that the results of this study showed that there was no significant difference between the intervention group (surfactant + budesonide) and the control group (surfactant only) in some outcomes and it was not in line with the results of other similar studies, several possible reasons can be presented for this:

1 - Limited sample size and high variability of outcomes: One of the debatable points about the current study is its sample size. This study was conducted on 60 infants (30 in each group). Although this sample size is common in clinical studies, the statistical power of the study may not have been sufficient to detect possible differences between the two groups. Some of the outcomes investigated in the present study (such as intraventricular bleeding, mortality, etc.) have high variability and are affected by several factors (fluctuation in blood pressure & CO<sub>2</sub> and severe prematurity and etc.). This may have led to the non-recognition of a significant difference between the two groups.

2- Other factors, such as the clinical condition of the neonate and level of neonatal care, may have influenced the results, potentially affecting the results.

Overall, the results of the present study showed that the use of intratracheal surfactant along with budesonide can be effective in reducing the duration of ventilation compared to surfactant alone. However, this treatment approach did not have much effect on other outcomes of RDS. Therefore, more studies (multicenter) to investigate the effectiveness of other treatment methods such as surfactant + inhaled budesonide, less invasive

surfactant + budesonide administration techniques, other corticosteroid and stem cell or novel anti-inflammatory agents instead of budesonide which might provide additional benefits in preventing RDS and BPD in preterm infants.

### Research limitations

1 - One of the challenges of this study was related to the collection of samples. Many parents wanted to discharge their child from the hospital before the end of the treatment period. This slowed down the data collection process. Also, some parents were against the treatment plan of the randomized clinical trial. In the current study, all parents were thoroughly counseled that participation was entirely voluntary and that they could withdraw their child at any time without any impact on the standard of care provided. We provided clear information about both treatment arms and avoided promoting one intervention over another to minimize bias.

### Future implication or research needs

The current study suggests that combining surfactant with budesonide have potential benefits over surfactant alone in treating neonatal RDS, however, further research is required to determine optimal dose and method of administration for budesonide when used with surfactant. Also it is recommended that this study be expanded to a broader geographic area with a larger sample size. Future studies should also consider a longer follow-up period, such as one or two years, to assess the developmental outcomes of these infants.

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12884-025-08497-w>.

Supplementary material 1.

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### Authors' contributions

"Z.J., M.H.M.F., L.Sh., B.B., F.S., M.E., M.N. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. H.A. carried out the initial analyses. F.K.R. drafted the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work."

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### Data availability

No datasets were generated or analysed during the current study.

### Declarations

#### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (code: IR.KMU.AH.REC.1402.156). Also, it was registered in the clinical trial system (clinical trial ID: IRCT20211218053444N3).

#### Consent for publication

Written informed consent was obtained from all parents of the patients.

#### Competing interests

The authors declare no competing interests.

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