

# LATE SURFACTANT REPLACEMENT THERAPY AND ITS EFFICACY ON SEVERE BRONCHOPULMONARY DYSPLASIA IN NATIONAL CHILDREN HOSPITAL

Nguyen Thi Quynh Nga✉, Nguyen Thi Van  
Hanoi Medical University

*Bronchopulmonary dysplasia (BPD) is a chronic lung disease that is most commonly seen in premature infants who require prolonged mechanical ventilation and oxygen therapy. 75% of intubated infants have episodes of dysfunctional surfactants associated with lower levels of surfactant proteins. This study aims to evaluate the effectiveness of late surfactant therapy in treating BPD in premature infants. Nineteen preterm infants diagnosed with severe BPD requiring mechanic ventilation, according to Jobe and Bancalari, were treated with surfactant (Poractant alpha 100mg/kg intra-tracheal). Patients were observed for change in oxygen requirement before and at 1-h, 6-h, 12-h, 24-h, and 48-h after treatment. There were 13 boys and 6 girls; boy to girl ratio was 2.16/1. The mean gestation age was  $28.3 \pm 2$  weeks; the mean birth weight was  $1134.7 \pm 314$  gram. There was an increase in  $SpO_2$  (saturation of peripheral oxygen),  $PaO_2$  (the partial pressure of oxygen in arterial blood) and reduction in  $FiO_2$  (fraction of inspired oxygen),  $PaCO_2$  (the partial pressure of carbon dioxide in arterial blood),  $OI$  (oxygen index),  $MAP$  (mean airway pressure) and  $AaDO_2$  (Alveolar-to-arterial oxygen gradient) after surfactant ( $p < 0.05$ ). Conclusion: In patients with severe BPD, late surfactant therapy has shown initial benefits in lung functions and reducing oxygen requirement.*

**Keywords:** bronchopulmonary dysplasia, premature infants, late surfactant therapy.

## I. INTRODUCTION

Bronchopulmonary dysplasia (BPD) in preterm babies under 32 weeks of gestational age is defined as the dependence on oxygen at least 28 days after birth and classified into mild, moderate, and severe BPD according to the level of oxygen requirement and mode of pressure support. BPD is the most common long-term respiratory morbidity of premature infants. The reported global incidence range of BPD in extremely preterm infants was 10 - 89%, depending on region, gestational age, and birth weight.<sup>1</sup> The advances in neonatal care have improved the survival rate of extremely preterm

and low birth weight infants, leading to an increase in BPD cases.<sup>2</sup> BPD causes long-term respiratory, cardiovascular, and neurological complications from early childhood to adulthood and is a significant burden for the health care system, especially in low- and middle-income countries.

BPD in preterm infants results from lung injury from the inflammation process, mechanical ventilation, and exposure to high concentrations of oxygen during treatment of respiratory distress syndrome.<sup>3</sup> Thus, different therapeutic approaches have been proposed for treating BPD, including postnatal corticosteroids, antioxidant treatments, and appropriate ventilation strategies to reduce barotrauma and volutrauma. However, the efficacy of these therapies is still controversial.<sup>4</sup> Previous reports found that 75% of intubated

Corresponding author: Nguyen Thi Quynh Nga  
Hanoi Medical University

Email: ngaquynh2006@gmail.com

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infants have episodes of dysfunctional surfactant associated with lower levels of surfactant proteins, particularly SP-B.<sup>5,6</sup> Some small studies have shown the promising effect of late surfactant therapy in improving the respiratory severity score and reducing respiratory morbidity before one year of age.<sup>7,8</sup> The object of our study is to test the hypothesis that late surfactant administration has benefits in preterm patients with established BPD.

## II. METHODS

### 1. Study design

This case series study was conducted in the Neonatal Department of National Children

Hospital from 11/2015 to 10/2016 and approved by the Hospital Ethics Committee. Written consent from parents or legal guardians was obtained before the study.

### 2. Inclusion Criteria

Neonates were eligible if they were diagnosed with BPD according to Jobe and Bancalari definition<sup>9</sup>: preterm infants required oxygen at least 21% for at least 28 days and had severe respiratory failure needed invasive mechanical ventilation at the time of diagnosis.

### 3. Exclusion Criteria

BPD infants with infections and patent ductus arteriosus.

**Table 1. Definition of bronchopulmonary dysplasia: Diagnostic criteria<sup>9</sup>**

Gestational age (GA)	< 32 week	≥ 32 week
The time point of assessment	36 week postmenstrual age (PMA) or discharge to home, whichever comes first	> 28 days but < 56 days postnatal age or discharge to home, whichever comes first
Oxygen requirement	Treatment with oxygen > 21% for at least 28 days	
Mild BPD	Breathing room air at 36-week PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need for < 30% oxygen at 36-week PMA or discharge, whichever comes first	Need for < 30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥ 30% oxygen and/or positive pressure at 36-week PMA or discharge, whichever comes first	Need for ≥ 30% oxygen and/or positive pressure at 56 days postnatal age or discharge, whichever comes first

### 4. Study procedures

- All preterm infants with gestational age under 37 weeks were assessed at 28 days old to diagnose BPD. There were 80 patients eligible, according to Jobe and Bancalari definition. Among them, 19 patients with severe BPD requiring mechanical ventilation were selected to administrate surfactant. Before surfactant administration, the patient oxygen status and ventilation setting were recorded.

- The surfactant product we used was portent alfa (Curosurf) with a 100mg/kg dosage and was given via endotracheal tube.

- Early outcomes of surfactant treatment were evaluated via respiratory indices, including:

+ Ventilation setting: fraction of inspired oxygen ( $FiO_2$ ), mean airway pressure (MAP), oxygen index (OI).

+ Blood oxygen status: saturation of peripheral oxygen ( $SpO_2$ ), partial pressure of oxygen in arterial blood ( $PaO_2$ ), the partial pressure of carbon dioxide in arterial blood ( $PaCO_2$ ), alveolar to arterial oxygen pressure difference ( $AaDO_2$ ).

- These values were carried out using arterial blood gas values and ventilator parameters of the infants before and 1-hour, 6-hour, 12-hour, 24-hour, 48-hour after surfactant administration.

OI and MAP were calculated using the following equation:

$$OI = (MAP \times FiO_2 \times 100) / PaO_2$$

$$MAP = [(PIP \times TI) + (PEEP \times TE)] / (TI + TE)$$

$$AaDO_2 = \{713 \times FiO_2 - PaCO_2 / 0.8\} - PaO_2$$

PIP: peak inspiratory pressure ( $cmH_2O$ )

TI: time of inspiration (sec)

PEEP: positive end expiratory pressure ( $cmH_2O$ )

TE: time of expiration (sec)

- Complications right after administration (regurgitation of surfactant, cyanosis/apnea, pneumothorax, pulmonary hemorrhage) were recorded. The outcome was death among the study population was noted as well.

### 5. Statistical analysis

Data were analyzed by using SPSS version 16.0 software. A Chi-squared test was used to compare categorical variables. T-test was used to compare means, and paired-samples T-test was used to compare means before and after treatment. The value of p is less than 0.05 was considered significant.

## III. RESULTS

### 1. General characteristics of the study population

From 11/2015 to 10/2016, there were 80 patients with BPD in our department. Nineteen patients with severe BPD requiring invasive mechanical ventilation were recruited into the study and received late surfactant therapy. There were 13 boys and 6 girls; boy to girl ratio was 2.16/1.

The mean birth weight of patients was  $1134.7 \pm 314$  g, with the proportion of low birth weight ( $< 1000g$ ), low birth weight (1000 - 1500g), and low birth weight (1500 - 2500g) were 47.4%, 42.1%, and 10.5%, respectively. The mean gestational age was  $28.3 \pm 2$  weeks. The proportion of highly preterm (GA  $< 28$  weeks), very preterm (GA 28 - 32 week), and moderately preterm (GA 32 - 34 week) were 42.1%, 52.6%, and 5.3%, respectively. The surfactant was given at  $30 \pm 3.1$  days with corrected age was  $32.4 \pm 3$  weeks of postmenstrual age and the mean weight at the time of surfactant administration was  $1512 \pm 213$  g.

### 2. Effect of surfactant administration on lung functions

Before the surfactant treatment, mean  $SpO_2$ ,  $FiO_2$ ,  $PaO_2$ ,  $PaCO_2$ , MAP, OI and  $AaDO_2$  values were as follows: 89.95; 54.68; 43.32; 48.42; 9.47; 11.74; 283.1 respectively. Ventilator settings were adjusted with arterial blood gas results.  $SpO_2$ ,  $PaO_2$  values significantly increased. Whereas  $FiO_2$ , MAP, OI,  $AaDO_2$  values significantly decreased at 1-hour, 6-hour, 12-hour, 24-hour, 48-hour ( $p < 0.05$ ).  $PaCO_2$  slightly increased after 1-hour and 6-hour, followed by significant decreases ( $p < 0.05$ ).

### 3. Complications of treatment

During 48h after surfactant administration,

we did not witness any complications. In term of death, in 19 patients received late surfactant treatment, one patient died after one week. After three weeks, 17 patients survived, and at the time of discharge, 12 patients had a full recovery. The cause of death was a nosocomial infection.

#### IV. DISCUSSION

In 19 patients who received late surfactant therapy, the percentage of male patients was higher than that of female patients; the male to female ratio was 2.16/1. Mean gestational age was  $28.37 \pm 2$  weeks, and the mean birth weight was  $1134.74 \pm 314$  gram. Our results were higher than the results of Pandit et al.<sup>10</sup> The difference may be due to the difference in the study population.

Respiratory distress syndrome (RDS) after birth resulted from a deficiency of pulmonary surfactant in preterm infants. Intratracheal exogenous surfactant replacement therapy reduces mortality, air leak, and the need for respiratory support in mechanically ventilated premature infants. Early rescue is defined as surfactant treatment within 1 to 2 hours of birth, and late rescue is defined as surfactant treatment two or more hours after birth.

Many risk factors for BPD include premature birth, respiratory failure, oxygen supplementation, and mechanical ventilation. Merrill et al. (2004) conclude that most premature infants requiring continued respiratory support after seven days of age experience transient episodes of dysfunctional surfactant associated with a deficiency of SP-B and SP-C5. It was assumed that surfactant would improve lung function in premature infants with BPD to observe a change of respiratory parameters after surfactant administration to them.<sup>5</sup> Digeronimo et al. found that mechanical ventilation could down-regulate surfactant protein expression.<sup>11</sup>

The use of surfactants for this indication has not been reported in the literature before. Within 48 hours of treatment with a surfactant, we observed improvements in lung functions by reducing the need for supplemental oxygen, as evidenced by the reduction of FiO<sub>2</sub> supply and the increase in SpO<sub>2</sub>, which were shown in Figure 1. The difference was significant with  $p < 0.05$ . Our results were similar to Pandit et al. study, and the improvement persisted for 72 hours after administration.<sup>10</sup> The study of Jean-Michel Hascoë shown similar results in terms of FiO<sub>2</sub> supply.<sup>8</sup>

The change in blood oxygenation proved the improvement of lung functions. The PaO<sub>2</sub> increased stably after surfactant administration and remained at  $66.42 \pm 13.86$  mmHg at 48-hour after treatment. Although this was not a high PaO<sub>2</sub>, it was acceptable in preterm infants with BPD to prevent retinopathy of premature.

The difference between oxygen index (OI) and mean airway pressure (MAP) was witnessed in our study. After installing surfactant, we found that both OI and MAP experienced a downward trend, sharply in the first hour and then gradually for 48 hours after treatment. The differences were significant with  $p < 0.05$ . These findings can imply that there was an improvement in lung compliance after treatment. Katz et al. showed that lung function was improved up to 48 hours after surfactant instillation in infants receiving one repeated dose of surfactant for respiratory failure after six days.<sup>6</sup>

The different change in the partial oxygen pressure between the alveoli and the arteries (AaDO<sub>2</sub>) was also noted. There was a sustainable drop in AaDO<sub>2</sub> after surfactant therapy. The reduction was significant with  $p < 0.05$ . The change in AaDO<sub>2</sub> referred that the alveolar-capillary barrier had a better stretch

for better air diffusion. Other studies have also shown a similar result.<sup>7,10</sup>

During and after surfactant administration, we witnessed no adverse events of treatment like apnea, pneumothorax. The mortality rate in the study population was 36.8%. The cause of all death was a nosocomial infection. It implied that the mortality rate of BPD was high, and repeat surfactant therapy might not improve the mortality rate.

The limitation of our study related to a small study population so that the risk factors of severe BPD were not fully identified. We did not include these patients' long-term follow-up to evaluate the chronic lung diseases related to BPD.

## V. CONCLUSION

The employment of late surfactant therapy in patients with severe BPD improved lung functions and reduced oxygen requirement. Further studies need to be done to evaluate the efficacy of surfactant therapy on the long-term management of BPD.

## ABBREVIATION

AaDO <sub>2</sub>	The alveolar to the arterial oxygen pressure difference
BPD	Bronchopulmonary dysplasia
FiO <sub>2</sub>	Fraction of inspired oxygen
MAP	Mean airway pressure
OI	Oxygen index
PaCO <sub>2</sub>	The partial pressure of carbon dioxide in arterial blood
PaO <sub>2</sub>	The partial pressure of oxygen in arterial blood
SpO <sub>2</sub>	Saturation of peripheral oxygen

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