

## **Influence of comprehensive management after discharge on short-term prognosis of very preterm infants with bronchopulmonary dysplasia.**

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### **Abstract**

**Objective:** To evaluate the influence of comprehensive management after discharge upon the short-term prognosis of very preterm infants diagnosed with bronchopulmonary dysplasia (BPD).

**Methods:** Very preterm infants surviving  $\geq 28$  d, admitted to NICU of the First Hospital Affiliated of Sun Yat-sen University between January 2013 and October 2014 were selected in this investigation. All infants were assigned into BPD and non-BPD groups. After hospital discharge, standard follow-up and early intervention were delivered. Physical signs, nervous system development and the incidence of respiratory tract symptoms were statistically compared between two groups.

**Results:** A total of 76 very preterm infants were eligible for inclusion including 39 (51.3%) infants with BPD and 37 (48.7%) non-BPD. No death, blindness or brain paralysis was noted in either group. The body weight, length and percentage of catch-up growth at corrected age of 3-, 6- and 12-month did not significantly differ between the BPD and non-BPD groups ( $P \geq 0.05$ ). The frequency of pneumonia complication, asthma episode and readmission in the BPD group was significantly higher compared with that in the non-BPD group (all  $P < 0.05$ ).

**Conclusion:** Comprehensive management after discharge can enhance the short-term prognosis of very preterm infants complicated with BPD, accelerate catch-up growth and decrease the risk of poor prognosis of nervous system disorders, whereas fail to reduce the incidence of respiratory tract symptoms.

**Keywords:** Management after discharge, Follow-up, Bronchopulmonary dysplasia, Very preterm infants, Prognosis.

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### **Introduction**

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease that severely affects preterm infants (especially very preterm infants). Recently, along with the increasing survival rate of low-weight and very low-weight infants, the incidence of BPD complication has been elevated [1]. BPD is characterized with high death rate and risk of clinical complications. Moreover, BPD infants may suffer from feeding difficulty, apnea, hypoevolutism, long-term cognitive dysfunction and brain paralysis [2], which severely influences the survival and prognosis of preterm infants. How to establish systematic management and implement early intervention plays a pivotal role in improving the prognosis of very preterm infants. In this study, comprehensive management after discharge was standardized, aiming to effectively reduce the incidence of respiratory system diseases, hypoevolutism and brain paralysis in very preterm infants complicated with BPD.

### **Materials and Methods**

#### **Baseline data**

Very preterm infants surviving  $\geq 28$  d (gestational age  $< 32$  weeks) [3], admitted to the Neonatal Intensive Care Unit (NICU) of the First Hospital Affiliated of Sun Yat-sen University between January 2013 and October 2014 were selected in this investigation. All infants were assigned into BPD and non-BPD groups. Exclusion criteria: (1) Length of hospital stays  $< 28$  d; (2) Those with severe congenital malformations or hereditary metabolism disorders; (3) Those with congenital malformation that affects lung development, requiring oxygen inhalation due to respiratory tract obstruction.

#### **Diagnostic criteria and clinical staging of BPD**

In a BPD seminar held in June 2000, National Institute of Child Health and Human Development (NICHD), National Heart, Lung, and Blood Institute and National Organization for Rare Disorders according to the latest definition of BPD collectively proposed that BPD is defined as the neonates treated with more than 21% oxygen for at least 28 days [4].

**Clinical staging of BPD:** The staging of BPD was evaluated based on the need for oxygen before 36 weeks post-menstrual age or discharge for babies born before 32 weeks. (1) Mild: No need for oxygen inhalation; (2) Moderate:  $\text{FiO}_2 < 30\%$ ; (3) Severe:  $\text{FiO}_2 \geq 30\%$  or need for mechanical ventilation.

### Management after hospital discharge

- 1) Prior to hospital discharge, the parents of the affected infants were informed with the potential problems, processing method and assistance hotline. The importance of regular follow-up should be emphasized. The parents were informed with the follow-up plan at 1 week after discharge for the infants at corrected age of 1, 2, 3, 4, 5, 6, 9, 12, 18 and 24 months.
- 2) The nurses should deliver nursing and emergent care training to the parents and teach them how to observe the presence of cyanosis, dyspnea and emergent management of milk choking and apnea.
- 3) For the infants requiring oxygen therapy after hospital discharge, the guardians should master the operation of oxygenerator.
- 4) The chief nurse should conduct follow-up by telephone, offer nursing care guidance and remind the parents of the follow-up time.
- 5) Coordinating work among multiple disciplines should be accomplished. NICU physicians were responsible for outpatient follow-up and collecting the information of feeding method and problem, bronchopneumonia complication, frequency of asthma episode, frequency of readmission due to respiratory tract infection, family history of allergy, history of eczema and allergic history of milk protein by questionnaire survey. Physical growth and nerve system development should be regularly evaluated. The nurses should provide guidance upon nutrition reinforcement, intelligence development and intervention measure of activity development. Those infants with nervous system development retardation were transferred to the Department of Rehabilitation. Those complicated with feeding difficulty and body weight lower than normal counterparts by the third percentile were given with nutrition reinforcement regime established and adjusted by the Department of Nutrition. The physicians from the Department of Ophthalmology and Otolaryngology participated in the follow-up for fundus, visual acuity and hearing tests.
- 6) The follow-up record of all infants was established and managed by the designated staff [5].

### Statistical analysis

SPSS 13.0 statistical software was utilized for data analysis. Normally-distributed measurement data were statistically compared between two groups by using t-test. Non-normally-distributed measurement data were compared by rank-sum test between two groups. Enumeration data were statistically compared by using chi-square test. A value of  $P < 0.05$  was considered as statistically significant.

## Results

### Baseline data

**Incidence of BPD in very preterm infants between 2013 and 2014:** In total, 689 preterm infants were admitted to the NICU of our hospital between January 2013 and October 2014 and 106 of whom were very preterm infants. Seventy six infants were eligible for the inclusion criteria, 39 cases complicated with BPD with an incidence of 51.3%. Twenty infants (51.3%) were diagnosed with mild BPD, 17 (43.6%) with moderate BPD and 2 with severe BPD (5.1%).

**Table 1.** Perinatal period conditions and clinical outcome between the BPD and non-BPD groups.

Variable	BPD group (n=39)	Non-BPD group (n=37)	$\chi^2$ value/t value	P value
Female n(%)	16 (41.0)	17 (45.9)	0.187	0.712
GA (w, $\bar{x} \pm s$ )	29.7 ± 1.5	31.2 ± 1.0	-4.515	0.000
BW (kg, $\bar{x} \pm s$ )	1.26 ± 0.28	1.47 ± 0.22	-3.63	0.010
Antenatal use of dexamethasone	25 (64.1)	29 (78.4)	1.88	0.175
SGA n (%)	7 (17.9)	10 (22.4)	0.889	0.342
EUGR upon hospital discharge (according to body weight) n (%)	19 (48.7)	13 (35.1)	1.418	0.230
EUGR upon hospital discharge (according to head circumference) n (%)	24 (61.5)	12 (32.4)	6.367	0.010

**Table 2.** Comparison of treatment during hospitalization between the BPD and non-BPD groups.

Variable	BPD group n=39	Non-BPD group n=37	$\chi^2$ value/t value	P value
Mechanical ventilation time >7 d n (%)	13 (33.3)	2 (5.4)	9.225	0.001
Mechanical ventilation time (d, $\bar{x} \pm s$ )	9.5 ± 9.2	2.5 ± 1.5	4.680	0.000
Use of PS n (%)	36 (92.3)	33 (89.2)	0.221	0.656
Oxygen concentration (>30%) >7 d n (%)	19 (48.7)	1 (2.7)	20.460	0.000
Time of oxygen use (d, $\bar{x} \pm s$ )	48.6 ± 17.7	16.5 ± 7.3	10.391	0.000

Perinatal period conditions and clinical outcome after hospital discharge between the BPD and non-BPD groups were illustrated in Table 1. The mean gestational age and birth weight in the BPD group were significantly lower than those in the non-BPD group (both  $P < 0.05$ ). Upon hospital discharge, the percentage of extrauterine growth retardation (EUGR) according to head circumference in the BPD group was

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significantly higher compared with that in the non-BPD group ( $P<0.05$ ).

Treatment of very preterm infants during hospitalization between the BPD and non-BPD group were illustrated in Table 2. The time of mechanical ventilation and oxygen use in the BPD group was significantly longer compared with that in the non-BPD group (both  $P<0.05$ ). The percentage of mechanical ventilation time  $>7$  d and time of oxygen use ( $>30\%>7$  d was considerably higher compared with those in the non-BPD group (both  $P<0.05$ ).

### **Follow-up of very preterm infants between BPD and non-BPD groups**

The follow-up endured until the corrected age of 12 months. No follow-up loss occurred in either group. Nutrition reinforcement feeding was delivered strictly according to the doctor's advice and adjusted based on the growth conditions after discharge. No cases of death, brain paralysis or blindness were noted in two groups. In the BPD group, 5 infants required for intermittent oxygen inhalation during breast feeding. The follow-up outcomes were illustrated in Tables 3 and 4. Body weight and the percentage of body length  $>P10$  at corrected age of 3, 6 and 12 months did not significantly differ between two groups (both  $P \geq 0.05$ ). However, the frequency of complicated pneumonia, asthma episode and readmission in the BPD group was considerably higher compared with that in the non-BPD group (all  $P<0.05$ ).

**Table 3.** Comparison of follow-up data between the BPD and non-BPD groups Part 1.

Parameter	BPD (n=39)	Non-BPD (n=37)	X <sup>2</sup> value/t value	P value
Family history of allergy n (%)	8 (20.5)	11 (29.7)	0.849	0.353
History of eczema n (%)	7 (17.9)	4 (10.8)	0.557	0.452
History of milk protein allergy n (%)	6 (15.4)	4 (10.8)	0.350	0.554
Frequency of complicated pneumonia ( $\bar{x} \pm s$ )	1.54 1.144	$\pm$ 0.32 0.475	$\pm$ 47.908	0.000
Frequency of asthma episode ( $\bar{x} \pm s$ )	1.46 1.536	$\pm$ 0.35 0.484	$\pm$ 83.217	0.000
Frequency of readmission ( $\bar{x} \pm s$ )	0.72 0.875	$\pm$ 0.14 0.347	$\pm$ 27.425	0.000
Feeding problem n (%)	15 (45.5)	16 (43.2)	0.034	0.853

**Table 4.** Comparison of follow-up data between the BPD and non-BPD groups Part 2.

Parameter	BPD (n=39)	Non-BPD (n=37)	X <sup>2</sup> value/t value	P value
Body weight $>P10$ n (%)				

at corrected age of 3 months	20 (51.3)	27 (73.0)	3.834	0.050
at corrected age of 6 months	26 (66.7)	31 (83.9)	3.019	0.062
at corrected age of 12 months	29(74.4)	32(86.5)	1.740	0.180
Body length $>P10$ n (%)				
at corrected age of 3 months	19 (48.7)	22 (59.5)	0.882	0.412
at corrected age of 6 months	25 (64.1)	28 (75.7)	1.205	0.289
at corrected age of 12 months	30 (76.9)	29 (78.4)	0.023	0.902
Head circumference $>P10$ n (%)				
at corrected age of 3 months	21(53.8)	28 (75.7)	4.009	0.045
at corrected age of 6 months	24 (61.5)	32 (86.5)	6.014	0.012
at corrected age of 12 months	27 (69.2)	34 (91.6)	6.074	0.011

\*P10 denotes lower compared with normal counterparts by the 10<sup>th</sup> percentile

## Discussion

BPD is one of the most severe complications occurring in preterm infants, especially very preterm infants. BPD is characterized with high mortality. Previous studies have demonstrated that the mortality rate of severe BPD is up to 25% and 10% in the first year after onset. The causes of death mainly include recurrent lower respiratory infection (dominantly respiratory syncytial virus), septicemia, persistent pulmonary hypertension, pulmonary heart disease and sudden death [5]. The admission rate of the survived BPD infants attains up to 50% [6], which severely affects the survival rate and quality of life.

In our hospital, the incidence of BPD has tended to elevate in recent years. The incidence of BPD was up to 51.3% between 2013 and 2014, higher than that in previous multi-center investigations in China [7]. The higher incidence in our center is probably correlated with the high percentage of pregnant woman with severe diseases and very preterm infants. At present, multiple methods including prenatal application of glucocorticoid, postnatal substitution therapy of exogenous surface-active substance and protective ventilation strategy have been widely adopted to prevent and treat BPD during hospitalization. Besides, standard systematic management and nutrition reinforcement intervention have captivated more and more attention to improve clinical prognosis and reduce death rate.

It has been widely accepted that preterm infants must be followed up within the first 2 years after birth to evaluate nervous system development and physical growth [5,8]. In developed countries, systematic investigations related to preterm infant follow-up have been established to provide

certain reference for treatment and rescue of preterm infants, especially those complicated with BPD [5,9]. In China, however, relevant follow-up studies have been rarely performed, especially long-term follow-up, which severely limits evaluating upon clinical efficacy and subsequent therapy and probably misses the optimal opportunity of early intervention [10]. Previous investigations have indicated that the risk of EUGR in preterm infants, especially those complicated with BPD and very low birth weight, is high [9]. Approximately 30~67% of BPD affected infants presented with growth retardation after hospital discharge [11]. Consequently, nutrition reinforcement and supplement play a vital role in catch-up growth and repairing of tissues and organs. In our hospital, follow-up studies of high risk infants have been conducted for a decade. In recent 5 years, comprehensive management of very preterm infants after discharge have been gradually standardized, especially nutrition reinforcement, which yield favorable clinical efficacy. The findings in this study revealed that although the BPD infants presented with younger gestational age, lower body weight and longer mechanical ventilation compared with non-BPD counterparts, the body weight and length and the percentage of catch-up growth did not differ from those of non-BPD group. At corrected age of 6 months, over 60% of infants completed catch-up growth, suggesting the pivotal role of nutrition reinforcement for very preterm infants, especially those complicated with BPD following hospital discharge. At present, randomized control trial (RCT) and nutrition guideline specifically designed for BPD infants are not available [12]. The results in current trial suggested that over 20% of preterm infants failed to complete catch-up growth at corrected age of 12 months (especially the enlargement of head circumference). The amount of nutrients required for very preterm infants to complete catch-up growth and improve clinical prognosis remains debated [13].

Previous study [14] have demonstrated that premature delivery influences the long-term function of lung of preterm infants, even worse in preterm infants complicated with BPD, which is associated with the severity of diseases [15,16]. In this study, prenatal use of glucocorticoid and substitution therapy of surface-active substance did not significantly differ between the BPD and non-BPD groups. However, the frequency of complicated pneumonia, asthma episode and readmission in the BPD group was significantly higher compared with that in the non-BPD group ( $P<0.05$ ), which is consistent with overseas findings [17]. In this study, stratified analysis of BPD severity was not conducted due to small sample size. Lung function test was not performed. The time of follow-up was short. Consequently, after nutrition reinforcement, pulmonary function outcome, correlation with disease severity and long-term prognosis remain to be elucidated.

BPD is a high risk factor for brain development delay in preterm infants [18], which is associated with poor neurodevelopmental outcomes in preterm infants [19]. Additionally, no infants were complicated with brain paralysis or blindness, or died. These results may not only ascribe to systematic management after discharge and early intervention,

but also probably result from the sample size of very preterm and severe BPD infants. Taken together, comprehensive management after discharge could enhance the clinical prognosis of very preterm infants, accelerate catch-up growth and decrease poor prognosis of nervous system. However, it fails to reduce the incidence of respiratory tract symptoms.

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