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Position management on pulmonary function and bronchopulmonary dysplasia in premature infants: study protocol for a randomised controlled trial

Liu Yang ,[1] Zhengrong Bao,[2,3] Lianyu Zhang,[2,3,4] Xiaoping Lei ,[2,3,5] Lingping Zhang[2,3,4]

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LY and ZB contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Lingping Zhang;
zhanglingping717@swmu.edu.cn

ABSTRACT

Introduction Bronchopulmonary dysplasia (BPD) is a common disease caused by various factors and mechanisms in premature infants. Owing to lung hypoplasia and the lack of alveolar surfactants in premature infants, oxygen therapy is often needed to maintain adequate breathing. Nevertheless, prolonged oxygen therapy can easily induce BPD, and there is currently no effective treatment. Therefore, the prevention of BPD in premature infants during hospitalisation is essential. Studies have revealed that the prone position can effectively improve the oxygenation of premature infants. However, a few studies have reported whether prone positioning can improve lung function and reduce BPD incidence. This trial will determine whether the prone position, compared with the supine position, can reduce BPD incidence and improve lung function in preterm infants.

Methods and analysis This study protocol is for a single-centre, single-blind, randomised controlled trial of the prone position in premature infants. Following daily feeding, premature infants will be placed in the lateral position for 30 min; then they will be turned to the supine position (control group) or prone position (intervention group) for 2 hours each in the morning and afternoon. Moreover, infants in both groups will be placed in the supine or lateral position alternately according to their medical needs for the remaining time. The study begins when the premature infants are stable within 5 days after admission and ends when they are discharged from the hospital or at 36 weeks postmenstrual age. The primary outcome is the survival rate without BPD. The secondary outcomes include lung function parameters and lung oxygen saturation.

Ethics and dissemination This trial is approved by the ethics committee of the Affiliated Hospital of Southwest Medical University, (ref approval no.KY2021186). The results will be published in a peer-reviewed journal.

Trial registration number ChiCTR2100049847.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a study that aims to explore the correlation between the prone position and the incidence of bronchopulmonary dysplasia in preterm infants.
⇒ Attention needs to be given to the lung development of premature infants after birth. Plethysmography can reflect the development of alveoli. However, this method is relatively new and seldom used.
⇒ The process of plethysmography measurement is challenging, and the infant's agitation may affect the results.
⇒ This is a single-centre study, which may affect the reliability of the findings. Large, multicentre, randomised control trials are further required to validate our hypothesis.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that occurs mainly in preterm infants, which is caused by the imbalance between lung injury and the repair of the immature lung.[1] The risk of BPD is proportional to prematurity and low birth weight, both of which are the strongest predictors of BPD.[2] The structural and functional immaturity of the lung caused by prematurity, coupled with the use of some routine life-saving interventions, such as supplemental oxygen and mechanical ventilation, can lead to impaired lung reparative responses after birth.[2] The pathological features of BPD are mainly alveolar simplification and dysmorphic pulmonary vascularisation.[3] Infants with BPD exhibit highly variable clinical phenotypes. Some infants may or may not require respiratory support depending on the severity of the disease, others may be tachypneic and show signs of respiratory distress according to the degree of pulmonary oedema.[4]

The incidence of BPD varies significantly between hospitals, mainly due to differences in perinatal practices, management styles and the lack of a consistent definition of BPD.[4] Since BPD was first proposed in 1967, the definition of BPD has evolved and been revised many times due to the changing pathology and manifestations of the disease.[5 6] Adapted

to current BPD management practices, to better predict the long-term prognosis of very preterm infants, modern diagnostic criteria for BPD is classified according to the mode of respiratory support administered at 36 weeks postmenstrual age (PMA).[7]

The adverse effects of BPD on premature infants can persist into adulthood. From a functional perspective, a review reported that individuals with BPD exhibit significant airflow limitation during adolescence and adulthood, and their lung function may decline earlier and more dramatically during adulthood.[8] In addition, infants with BPD are at increased risk of cerebral palsy, neuropsychological impairment and developmental delay.[9 10] Therefore, before or after discharge, BPD-related complications pose vast and costly public health challenges.

The deficiency of surfactant in the immature lung, volutrauma and barotrauma caused by exposure to invasive mechanical ventilation, and pulmonary inflammation are important factors in the pathogenesis of BPD.[11] Avoiding invasive mechanical ventilation, minimising excessive oxygen administration, preventing infection and early extubation are important strategies to prevent BPD.[2 12 13] Studies have revealed that prone positioning effectively improves oxygenation.[14–16] When a premature infant is in the prone position, lung expansion occurs in the dorsal lung region and lung volume increases because compression of dorsal lung tissue by abdominal contents and the heart decreases.[17–19] A study showed that the dynamic elevation of end-expiratory lung volume decreased in the prone position; thus, providing additional evidence supporting this view earlier stated.[20] In addition, thoracoabdominal synchrony increased in the prone position,[20] which plays a key role in the efficiency of lung ventilation.[21 22] A study of people with respiratory distress syndrome showed that a change from the supine to the prone position significantly increased resting lung volumes and decreased dynamic lung strain.[23] Similarly, the prone position led to an inversion of the inflation gradient, resulting in a more uniform distribution of stress and strain in the lungs, preventing ventilator-induced lung injury.[24 25] Summarily, the prone position promotes lung oxygenation, affecting the respiratory support mode and oxygen supply for premature infants, thereby reducing risk factors for BPD. Thus, it seems reasonable to use a prone position to prevent BPD. Accordingly, a randomised controlled trial is needed to prove the efficacy and safety of this treatment.

METHODS AND ANALYSIS

Aim of the study

This randomised controlled study investigates whether the prone position can improve pulmonary development and reduce the incidence of BPD in premature infants.

Study design

This single-centre, single-blind, randomised controlled trial will be performed at the Affiliated Hospital of Southwest Medical University. We will recruit participants according to strict inclusion and exclusion criteria. Position management will be carried out on enrolled infants when their condition is stable, that is, under spontaneous breathing or respiratory support, the infant's percutaneous oxygen saturation (SpO_2) is maintained at 90%–94%[26 27] and no emergency symptoms occur (a sudden sharp drop in SpO_2, desaturation events and requiring neonatal resuscitation). Infants who do not initiate intervention within 5 days of enrolment will be excluded from this study.

The study will take place during the day shift to prevent accidents at night due to insufficient nurses. Premature infants will be placed in a lateral position for 30 min after feeding, then they will be turned to the supine position (control group) or prone position (intervention group) for 2 hours each in the morning and afternoon. During these periods in both groups, the nurses will stop turning and stimulating the infants to make them sleep stably. Moreover, infants in both groups will be placed in the supine or lateral position alternately according to their medical needs for the remaining time. The study will end when the premature infants are at 36 weeks PMA or are discharged from the hospital.

Participants

The inclusion criteria are gestational age <30 weeks or birth weight <1500 g. The exclusion criteria include any of the following conditions: severe structural abnormalities or chromosomal defects, severe hypoxic-ischaemic encephalopathy, periventricular haemorrhage grade III or IV, or active bleeding. The withdrawal criteria are withdrawal of informed consent by the parents or progressive worsening of the patient's condition.

Patient and public involvement

The patients or the public did not participate in the study design. The researchers will carefully explain the detailed processes, potential benefits and risks to the parents of the infants enrolled in this trial. Their parents will be requested to sign an informed consent form to indicate their willingness to participate voluntarily.

Sample size calculation

According to the data from the participating centre in previous years, the incidence of BPD in eligible infants was 42%, assuming that the incidence of BPD will reduce to 30% after the intervention. Adopting a maximum significance level of α=0.05 and a minimum test power of 80%, the number of participants needed per group is 247, which will be increased by 5% to compensate for possible withdrawals during the follow-up; hence, 518 cases are needed for enrolment, with 259 patients per group.

Randomisation

In this study, eligible patients will be numbered according to the order in which they are enrolled. They will be randomly grouped in a 1:1 ratio using the random number method. The randomisation results will be

sealed in a sequentially numbered envelope to ensure the blinding of group allocations. Five hundred and eighteen opaque envelopes will be packaged, the covers of which are numbered from 001 to 518, and the grouping results are placed in each corresponding numbered envelope in sequence. When an individual is enrolled, the researcher will obtain the corresponding envelope from the principal investigator and assign him or her to the corresponding group.

Outcomes and measurements

Primary outcome

The primary outcome is the survival rate without BPD at 36 weeks PMA, defined as infants with no therapeutic oxygen requirement at 36 weeks PMA. BPD severity is classified according to the following: grade 1, nasal cannula at flow rates ≤2 L/min; grade 2, nasal cannula at flow rates >2 L/min or non-invasive positive airway pressure; and grade 3, invasive mechanical ventilation.[7]

Secondary outcomes

Pulmonary function indexes

The pulmonary function test will be performed at 36 weeks PMA or before discharge, including tidal volume measurement and plethysmography. The Master Screen BabyBody Plethysmograph produced by the Jaeger company in Germany will be used for detection. The infant is tested 0.5–2 hours after feeding to ensure no abdominal distension. The equipment's barometric pressure, ambient temperature and volume are calibrated before the testing. The length and weight of infants are measured when they are in quiet sleep, and they are placed supine in the plethysmography box with their necks slightly extended to the back to keep their airways open. After cleaning the infant's mouth and nose secretions, the nurse tightens the infant's mask to cover the mouth and nose and ensure no air leakage. Data are collected five times for each test, manually removing the unqualified data (index variation coefficient >10%), and the computer automatically takes the average of the remaining data as the final result.

Lung regional oxygen saturation

Near-infrared spectroscopy (EGOS-600A/B/C near-infrared blood oxygen monitoring instrument, Suzhou FNGINMED, Beijing, China) is a non-invasive and easily applicable tool for monitoring tissue oxygen saturation and has been widely used in the neonatal intensive care unit. Placing probes on different areas of the infant's body, such as the forehead (cerebral), abdomen (mesentery) and lower back (renal), light source and photodetectors can measure tissue oxygen levels at different tissue depths to obtain the actual tissue oxygenation.[28] Currently, there are few studies on lung oxygen saturation, pulse oximetry alone is insufficient to reflect the lung oxygen condition of preterm infants and reveal whether there is enough blood flow or oxygen delivery to a particular tissue bed.[28] Studies have reported that for premature infants who received oxygen therapy, pulmonary oxygen saturation is more indicative of the actual oxygenation of the lung tissue, and clinical application can reduce the adverse conditions of excessive hypoxia or exposure to hyperoxia in the lungs of preterm infants.[29] Therefore, the nurses will measure the lung oxygen saturation of enrolled infants once a week in this study. The procedure is performed as follows: the nurse places the probe on the chest wall corresponding to the apex of the right lung of the premature infants, and after the curve is stable, three values are recorded to take the average value as the final result.

The outcomes at each time point will be collected by the investigators (table 1).

Clinical data collection

Baseline data, including maternal and infant characteristics, will be collected from the electronic medical record when the patient is enrolled. Maternal data include maternal age, maternal smoking history, gestational diabetes, assisted reproductive technology, mode of delivery, premature rupture of the membrane and placental abruption. Infant demographics include sex, gestational age, birth weight, 1 and 5 min Apgar scores, neonatal asphyxia and surfactant use.

Before and after the intervention every morning and afternoon, the researcher will obtain the patient's heart rate and SpO_2 data and instances of apnoeas during the hospital stay.

Information on the respiratory support mode and oxygen use time of premature infants who use a non-invasive ventilator, invasive ventilator or nasal cannula for oxygen inhalation during the study period will be obtained. The ventilator parameters will be collected, such as peak inspiratory pressure, positive end-expiratory pressure, mean airway pressure and the fraction of inspired oxygen.

The data on complications (such as pulmonary haemorrhage, sepsis and necrotising enterocolitis) and other diagnostic information of premature infants will be collected.

Data management

When a patient withdraws from the study, the previous data must be retained and the reason for withdrawal must be recorded. The data collected for participants until withdrawal will undergo intention-to-treat analysis. Two persons will record all data in case report forms (CRFs). The principal investigator will store other documents, such as informed consent, copies of medical records and original paper data in the filing cabinets. Related researchers have access to the anonymous data for future studies after application and permission. In addition, for sharing purposes, we will provide an utterly deidentified dataset to the appropriate data archive.

Table 1 SPIRIT: time points for enrolment, intervention and assessment

	Study period							
	Enrolment	Allocation	Post-allocation					Close-out
Timepoint	On admission	Stable condition	1 week after enrolment	2 weeks	3 weeks	4 weeks	Etc.	36 weeks PMA or before discharge
Enrolment								
Eligibility screen	√							
Informed consent	√							
Demographic data	√							
Allocation		√						
Intervention								
Prone position			√	√	√	√	√	
Supine position			√	√	√	√	√	
Assessment								
Baseline variables	√							
Primary outcome								√
Secondary outcomes								
Pulmonary function test								√
Lung oxygen saturation			√	√	√	√	√	

√, required; PMA, postmenstrual age; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

Statistical analysis

Statistical analysis will be performed using the SPSS V.19.0 (IBM). Categorical data will be presented as percentages (%) and compared using the χ^2 test. Continuous data with normal distribution will be presented as mean±SD and compared using the Student's t-test. Continuous data with abnormal distribution will be described as median and IQRs and analysed using the rank-sum test. Multivariate logistic regression will be performed to calculate the ORs and 95% CIs. A $p<0.05$ is considered statistically significant.

Midterm data analysis will be conducted after including the first 259 patients. If the prone position can significantly improve the lung function of premature infants or cause serious harm, the study will be terminated. The principal researcher will decide whether to take any other measures based on the results.

Data analysts will be blinded; an employee outside the research team will input data, but not group numbers into the computer in a separate datasheet; hence, the data analysts can analyse data without having to access allocation information. After data analysis results are obtained, the allocation data will be unblinded.

Ethics and dissemination

The research protocol is reviewed and approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (reference approval number KY2021186), and the ethics committee will oversee all procedures.

The researcher will notify the ethics committee in writing when the study is suspended or completed. Before making any changes to the research protocol, the principal researchers must submit a written application to the ethics committee and obtain new written informed consent from the parents.

The study results will be published in medical journals objectively and fairly. Confidentiality of the patient's information will be maintained, and personal information will not be disclosed unless relevant laws requirements. Government management departments, hospital ethics committees and related personnel can consult the patients' data following regulations when necessary. There are no plans to hire professional writers, and the final author list will be confirmed based on the authors' contributions to the research.

Quality control

To fully understand and master the standard operating procedures, we will train researchers on how to collect data before the start of the study. Face-to-face adherence reminder sessions and auditing will take place every week, and each of the data collection forms and the nature of the required information will be discussed in detail. Independent investigators at the Affiliated Hospital of Southwest Medical University will regularly monitor the quality of the data collected. If any error exists, researchers will be notified immediately.

Risk prevention

The prone position is a risk factor for sudden infant death syndrome; therefore, to prevent this, we will use continuous electrocardiograph monitoring, expand the range of alarm parameters and increase the alarm volume. One researcher will monitor the infant during the whole intervention period. Once hypoxia or cyanosis

occurs, neonatal resuscitation procedures will commence immediately.

Some complications may occur during the prone position, such as skin and mucous membrane damage, fluctuations in blood pressure caused by body position changes and compression of peripheral venous catheters. Researchers will observe the skin conditions of research participants daily. Once an adverse event occurs during the treatment, the time of occurrence, manifestations, treatment process and duration, and outcome of the adverse event will be recorded in detail on the CRFs. Participants can receive free treatment from the Affiliated Hospital of Southwest Medical University.

Trial status

Data collection will begin on 1 January 2022 and end on 31 December 2024. The protocol version number and date are as follows: the third edition, 15 November 2022.

Author affiliations
[1]School of Nursing, Southwest Medical University, Luzhou, Sichuan, China
[2]Department of Pediatrics, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China
[3]Department of Neonatology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China
[4]Clinical Nursing Research Institute, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China
[5]Department of Perinatology, Southwest Medical University, Luzhou, Sichuan, China

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ORCID iDs
Liu Yang http://orcid.org/0000-0001-6099-0542
Xiaoping Lei http://orcid.org/0000-0003-3818-7117

REFERENCES

1 Jobe AH, Models A. Animal models, learning lessons to prevent and treat neonatal chronic lung disease. *Front Med* 2015;2:49.
2 Kalikkot Thekkeveedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: a review of pathogenesis and pathophysiology. *Respir Med* 2017;132:170–7.
3 Coalson JJ. Pathology of new bronchopulmonary dysplasia. *Semin Neonatol* 2003;8:73–81.
4 Sahni M, Mowes AK. Bronchopulmonary Dysplasia. In: *StatPearls*. Treasure Island (FL): Copyright © 2022, StatPearls Publishing LLC, 2022.
5 Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357–68.
6 Bancalari E, Jain D. Bronchopulmonary dysplasia: 50 years after the original description. *Neonatology* 2019;115:384–91.
7 Jensen EA, Dysart K, Gantz MG, *et al*. The diagnosis of bronchopulmonary dysplasia in very preterm infants. an evidence-based approach. *Am J Respir Crit Care Med* 2019;200:751–9.
8 Carraro S, Filippone M, Da Dalt L, *et al*. Bronchopulmonary dysplasia: the earliest and perhaps the longest lasting obstructive lung disease in humans. *Early Hum Dev* 2013;89 Suppl 3:S3–5.
9 Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. *Semin Perinatol* 2006;30:227–32.
10 DeMauro SB. Neurodevelopmental outcomes of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 2021;56:3509–17.
11 Dumpa V, Bhandari V. Surfactant, steroids and non-invasive ventilation in the prevention of BPD. *Semin Perinatol* 2018;42:444–52.
12 Bhandari V. The potential of non-invasive ventilation to decrease BPD. *Semin Perinatol* 2013;37:108–14.
13 Vliegenthart RJS, Onland W, van Wassenaer-Leemhuis AG, *et al*. Restricted ventilation associated with reduced neurodevelopmental impairment in preterm infants. *Neonatology* 2017;112:172–9.
14 Eghbalian F. A comparison of supine and prone positioning on improves arterial oxygenation in premature neonates. *J Neonatal Perinatal Med* 2014;7:273–7.
15 Miller-Barmak A, Riskin A, Hochwald O, *et al*. Oxygenation instability assessed by oxygen saturation histograms during supine vs prone position in very low birthweight infants receiving noninvasive respiratory support. *J Pediatr* 2020;226:123–8.
16 Wells DA, Gillies D, Fitzgerald DA. Positioning for acute respiratory distress in hospitalised infants and children. *Cochrane Database Syst Rev* 2005;2:Cd003645.
17 Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 2000;161:1660–5.
18 Bhat RY, Leipälä JA, Singh NR-P, *et al*. Effect of posture on oxygenation, lung volume, and respiratory mechanics in premature infants studied before discharge. *Pediatrics* 2003;112:29–32.
19 Tawhai MH, Nash MP, Lin C-L, *et al*. Supine and prone differences in regional lung density and pleural pressure gradients in the human lung with constant shape. *J Appl Physiol* 2009;107:912–20.
20 Gouna G, Rakza T, Kuissi E, *et al*. Positioning effects on lung function and breathing pattern in premature newborns. *J Pediatr* 2013;162:37.e1:1133–7.
21 Elgellab A, Riou Y, Abbazine A, *et al*. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. *Intensive Care Med* 2001;27:1782–7.
22 Warren RH, Horan SM, Robertson PK. Chest wall motion in preterm infants using respiratory inductive plethysmography. *Eur Respir J* 1997;10:2295–300.
23 Aguirre-Bermeo H, Turella M, Bitondo M, *et al*. Lung volumes and lung volume recruitment in ARDS: a comparison between supine and prone position. *Ann Intensive Care* 2018;8:25.
24 Gattinoni L, Pesenti A, Carlesso E. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure: impact and clinical fallout through the following 20 years. *Intensive Care Med* 2013;39:1909–15.
25 Gattinoni L, Taccone P, Carlesso E, *et al*. Prone position in acute respiratory distress syndrome. rationale, indications, and limits. *Am J Respir Crit Care Med* 2013;188:1286–93.
26 Sweet DG, Carnielli V, Greisen G, *et al*. European consensus guidelines on the management of respiratory distress syndrome - 2019 update. *Neonatology* 2019;115:432–50.
27 Saugstad OD. Oxygenation of the immature infant: a commentary and recommendations for oxygen saturation targets and alarm limits. *Neonatology* 2018;114:69–75.
28 Marin T, Moore J. Understanding near-infrared spectroscopy. *Adv Neonatal Care* 2011;11:382–8.
29 Yang X, Lei X, Zhang L, *et al*. The application of near-infrared spectroscopy in oxygen therapy for premature infants. *J Matern Fetal Neonatal Med* 2020;33:283–8.