

Surgical ligation, not transcatheter closure, associated with a higher severity of bronchopulmonary dysplasia in extremely preterm infant intervened for patent ductus arteriosus

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Abstract

Objective: Patent ductus arteriosus (PDA) is a common complication among premature infants, and it may be responsible for prematurity-related complications, such as bronchopulmonary dysplasia (BPD). It is unclear whether different interventional methods contribute to the severity of BPD. To date, surgical ligation and the transcatheter approach have shown equal success in premature infants with hemodynamically significant PDA after medical treatment failure. Immediate improvement in the respiratory condition after transcatheter closure has been reported. However, the short-term pulmonary outcome has not been clarified yet. **Methods:** This retrospective study investigated infants born with a body weight less than 1000 g and underwent either surgical ligation or transcatheter closure of PDA in a single tertiary institution. The infants were divided into groups according to the type of procedure (surgical ligation or transcatheter occlusion). The primary outcome was the severity of BPD at discharge or at post-menstrual age of 36 weeks. The outcome was analyzed with logistic regression. **Results:** Forty-four patients met the inclusion criteria, and of these, 14 underwent transcatheter occlusion and 30 underwent surgical ligation. The overall birth body weight and gestational age ranges were not different. The univariate model revealed an association between the procedure type and BPD severity. The multivariate model confirmed associations of BPD severity with procedure type and severe respiratory distress syndrome requiring surfactant after adjusting for confounders. **Conclusion:** Compared with the transcatheter approach, surgery for PDA in extremely preterm infants is associated with severe BPD at discharge. Further large-scale studies are needed to determine the exact mechanism.

Title:

Surgical ligation, not transcatheter closure, associated with a higher severity of bronchopulmonary dysplasia in extremely preterm infant intervened for patent ductus arteriosus

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Abstract

Objective : Patent ductus arteriosus (PDA) is a common complication among premature infants, and it may be responsible for prematurity-related complications, such as bronchopulmonary dysplasia (BPD). It is unclear whether different interventional methods contribute to the severity of BPD. To date, surgical ligation and the transcatheter approach have shown equal success in premature infants with hemodynamically significant PDA after medical treatment failure. Immediate improvement in the respiratory condition after transcatheter closure has been reported. However, the short-term pulmonary outcome has not been clarified yet. **Methods :** This retrospective study investigated infants born with a body weight less than 1000 g and underwent either surgical ligation or transcatheter closure of PDA in a single tertiary institution. The infants were divided into groups according to the type of procedure (surgical ligation or transcatheter occlusion). The primary outcome was the severity of BPD at discharge or at post-menstrual age of 36 weeks. The outcome was analyzed with logistic regression. **Results :** Forty-four patients met the inclusion criteria, and of these, 14 underwent transcatheter occlusion and 30 underwent surgical ligation. The overall birth body weight and gestational age ranges were not different. The univariate model revealed an association between the procedure type and BPD severity. The multivariate model confirmed associations of BPD severity with procedure type and severe respiratory distress syndrome requiring surfactant after adjusting for confounders. **Conclusion :** Compared with the transcatheter approach, surgery for PDA in extremely preterm infants is associated with severe BPD at discharge. Further large-scale studies are needed to determine the exact mechanism.

Introduction

Patent ductus arteriosus (PDA) is a common cardiovascular complication among premature infants, and it may be responsible for prematurity-related complications. The ductus arteriosus is a vessel between the pulmonary circulation and systemic circulation in a fetus.¹ In most term infants, the ductus arteriosus closes spontaneously. However, in premature infants, the ductus often fails to close spontaneously. The spontaneous closure rate has been shown to be inversely related to the birth gestational age, and it ranges from 13% to 98%.²

In premature infants, a hemodynamically significant PDA has been reported to be associated with complications, such as pulmonary hemorrhage,^{3; 4} bronchopulmonary dysplasia (BPD),^{5; 6} intraventricular hemorrhage,^{7; 8} renal dysfunction, necrotizing enterocolitis,⁹ neurological impairments,¹⁰ and mortality.^{11; 12} A hemodynamically significant PDA will usually be treated with non-steroidal anti-inflammatory drugs,

such as ibuprofen and indomethacin. A PDA may fail to respond to medical treatment and may require non-pharmaceutical interventions. Surgical ligation is a well-established procedure for a PDA that has not responded to medical treatment. However, surgical ligation has been shown to be associated with the development of BPD.^{2; 13}

Recently, transcatheter interventions involving ductus arteriosus closure have been used in premature infants. Wang et al. reported the detailed process and experience of performing this technique in very low birth weight infants.¹⁴ Numerous studies have compared complications and success rates between transcatheter techniques and surgical ligation, and no statistically significant differences were noted. Furthermore, a comparison of the short-term effects after transcatheter techniques and those after PDA ligation revealed that transcatheter techniques improved the pulmonary score earlier. The authors reported the immediate benefits of respiratory trajectory following the transcatheter closure of PDA.¹⁵ However, the short-term impacts on the severity of BPD at discharge have not been reported, especially for extremely premature infants. Therefore, this retrospective study was conducted in a single institution to investigate the association between the different procedure types of PDA interventions and the severity of BPD among extremely premature infants requiring intervention for a hemodynamically significant PDA.

Material and Methods

2.1 Study Design

We performed a retrospective chart review of infants born with a body weight less than 1000 g and admitted to National Cheng Kung University Hospital from July 2014 to June 2020. We enrolled infants who received PDA invasive management involving either surgical ligation or transcatheter occlusion and were diagnosed with BPD at 36 weeks' post-menstrual age. Infants with BPD severity already classified before the procedure were excluded. According to the NICHD 2001 BPD diagnosis criteria, BPD was considered as 28 cumulative days of supplemental oxygen more than 21%. The severity of BPD was defined according to a previously published definition (Supplementary Table 1).¹⁶ Based on the type of intervention, patients were divided into a surgical ligation group (Group A) or a transcatheter occlusion group (Group B). The study protocol was approved by the Institutional Review Board (protocol code A-ER-109-137) of this institution.

2.2 Data Collection and Outcomes

We collected data on birth body weight, gestational age, fraction of oxygen (FiO₂) used before the procedure, sex, procedural body weight, procedural gestational age (PMA), invasive ventilation use, respiratory distress syndrome (RDS) requiring surfactant, and antenatal and post-natal steroid use. The research population recruitment algorithm is shown in Figure 1.

The outcome measurement of BPD severity involved classification as none, mild, moderate, or severe BPD or death before discharge, and severity was further divided into lower severity (none or mild BPD) and higher severity (moderate or severe BPD, or death).

Statistics and Analysis

All analyses were performed using SPSS (Version 28, IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered significant. Basic demographic data were compared with the Student's *t* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables as appropriate. The outcome analyses compared BPD severity between surgical ligation and transcatheter occlusion using logistic regression adjusted for selected risk factors. Two regression models were used for multivariate logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated.

Results

During the study period, a total of 66 patients received PDA interventions involving either transcatheter occlusion or surgical ligation, and 49 patients with a birth body weight less than 1000 g were included. Among these patients, 5 were excluded owing to BPD severity classified before the procedure. Thus, 44 patients met the inclusion criteria and were included (14 patients underwent transcatheter occlusion and 30 patients

underwent surgical ligation). The overall birth body weight ranged from 461 g to 979 g (transcatheter occlusion vs surgical ligation: 694.0 ± 117.9 g vs 655.9 ± 153.5 g, $p = 0.371$) and gestational age ranged from 22.43 weeks to 28.14 weeks (24.7 ± 1.4 weeks vs 24.3 ± 1.5 weeks, $p = 0.307$). The number of days from birth to treatment ranged from 3 to 92 days. The PMA at the procedure were not statistically different between the groups. Moreover, the FiO_2 values before the procedure were not different between the groups (transcatheter occlusion vs surgical ligation: 33.9 ± 10.3 vs 42.0 ± 25.7 , $p = 0.274$). Infants with RDS requiring surfactant instillation accounted for 79.5% of the total population, and the proportion was similar between the two groups. Detailed clinical variables are shown in Table 1.

Mild BPD was noted in 12 patients (5 in Group A and 7 in Group B), moderate BPD was noted in 24 patients (19 in Group A and 5 in Group B), and severe BPD was noted in 4 patients (all in Group A). Three patients died before the diagnosis of BPD was established or the severity was classified (1 in Group A and 2 in Group B). The BPD severity was further divided into lower severity (none or mild BPD) and higher severity (moderate or severe BPD, or death). The two-grade BPD severity was analyzed with logistic regression. The univariate model revealed an association between procedure type and BPD severity (Group A vs Group B, OR: 4.000, 95% CI: 1.009–15.862) (Table 2). After analyzing birth gestational age, sex, invasive ventilation use, FiO_2 used, RDS requiring surfactant, post-natal steroid treatment, and post-menstrual age, the multivariate model revealed associations of procedure type and RDS requiring surfactant with two-grade BPD severity in different logistic regression models adjusting for potential confounding variables (Table 3, Supplementary Table 2).

Discussion

The factors associated with BPD severity are heterogeneous. We hypothesized that chest wall damage and lung manipulation can affect the post-natal growth of the immature lung and hence can affect the severity of BPD at the timing of assessment. In this study, the basic characteristics of birth body weight, birth gestational age, surfactant use, antenatal and post-natal steroid use, post-menstrual weight, and age were similar between the groups. The multivariate logistic regression analysis showed associations of BPD severity with procedure type for PDA and RDS requiring surfactant. However, we failed to demonstrate differences related to birth gestational age or invasive ventilation before the procedure.

The use of antenatal steroids to prevent RDS and a conservative ventilation strategy have reduced the old form of BPD. However, a new form of BPD has been recognized as a developmental disorder.¹⁷ Lung growth enters the saccular stage at around 23 weeks of gestation, and the alveolar stage continues until adolescence.¹⁸ In this study, the majority of patients received antenatal steroids. Kulasekaran et al. and Chen et al. reported no difference in BPD incidence between males and females.^{19; 20} However, two previous studies reported a higher incidence in males.^{21; 22} In this study, male sex was not related to a poorer outcome.

This retrospective analysis revealed associations of surgery and surfactant use with BPD severity and mortality. As previously mentioned, the saccular stage occurs from approximately 26 to 36 weeks, and insult of the lung parenchyma may induce an inflammatory response and impair further maturation. Verhaegh et al. reported that median sternotomy for PDA ligation, in which the pleura was kept intact, was associated with a lower mean airway pressure after surgery compared with posterolateral thoracotomy. In addition, lower pneumothorax and atelectasis rate were observed.²³ Previous reports have suggested that thoracic surgery performed in the neonatal period may result in reduced post-natal lung growth^{24; 25} and a higher incidence of either restrictive or obstructive ventilatory defects after the surgery.²⁶ An animal model also demonstrated decreased lung compliance, decreased lung perfusion, and increased pulmonary vascular resistance after thoracotomy.²⁷ These findings indicate an undesirable impact on post-natal lung growth after thoracotomy. However, these studies focused on post-natal lung growth in term infants, and studies discussing how surgical thoracic manipulation affects preterm lung growth are limited. A report discussing the impact of surgery in very low birth weight infants showed an increased risk of death or neurodevelopmental impairment.²⁸ In contrast to term infants, premature infants are born primarily in the saccular stage. Insult to the lungs during this period may not only affect alveolarization but also impair epithelium gas exchange and airway resistance.

Gestational age at birth was not associated with BPD severity in this analysis; however, RDS requiring surfactant instillation was associated with BPD severity. This association reflects the actual degree of lung maturation and type II alveolar cell function. An immature alveolar epithelium is more likely to have surfactant deficiency and is more vulnerable to post-natal inflammatory insults. Owing to the widely acknowledged use of antenatal steroids to prevent RDS, the birth gestational age may not arbitrarily reflect maturation of the lungs.

Some potential mechanisms may explain our findings. In the physical aspect, a traumatic injury to the thoracic wall may induce growth impairments in the thoracic cavity, which can further inhibit lung growth. Scoliosis has been recognized as a sequela of thoracic surgery in the neonatal period.^{29; 30} Rib deformation after PDA ligation has also been reported.³¹ In addition, the pain after thoracic surgery may induce hypoventilation. It has been indicated that a low tidal volume after birth in preterm infants induces higher interleukin-8 and tumor necrosis factor- α (TNF α) levels compared with a normal volume. Moreover, the mechanical ventilator dependent period was longer in the low tidal volume group.³² In the biomedical aspect, manipulation of the lung during surgery causes some alveolar collapse, and there is rapid expansion after the surgery. This mechanical change generates a shearing force in the lung and causes mechanical injury,^{33; 34} which may induce inflammatory cytokine production, a mechanism similar to ventilator associated injury. In an animal model, TNF α , transforming growth factor- β , interleukin-6, and interleukin-11 were shown to be able to interfere with alveolarization.³⁵ Interleukin-6, -8, and -10 have been reported to be related to further BPD development and severity.^{36; 37} However, whether these cytokines contribute to or are induced by BPD is not well studied.

Several studies have reported an increased risk of BPD in preterm infants who have undergone PDA ligation.^{13; 38; 39} The safety and benefits of PDA ligation have been discussed recently, but consensus is lacking. Watchful waiting is an alternative approach for clinicians to deal with PDA after carefully weighing the benefits and risks.⁴⁰ Reports regarding conservative or surgical treatment for PDA have questioned the selection bias of the surgery group. In this study, we reported increased BPD severity and mortality after PDA ligation compared with transcatheter occlusion. The findings of this report contribute to the evidence that the drawback in PDA ligation may be related to the impact of lung or thoracic manipulation during surgery.

Some limitations of this study must be addressed. First, the study was retrospective in nature, and the assignment of the treatment was not randomized. Second, the number of participants in this study was small, and this small population may have limited the power of our analysis. Third, the clinical protocol of post-natal steroids varies among physicians and can be modified or repeated under clinical conditions. Fourth, although the statistical analysis showed no differences, infants in the transcatheter group had a larger body weight and PMA. In addition to the limitations of the study design, the transcatheter approach is a new technique, and the safety issue is still under debate.

Conclusion

Compared with transcatheter closure, surgical ligation for PDA in extremely preterm infants may be associated with increased severity of BPD. However, the exact mechanism needs to be determined through further large-scale studies and detailed biomedical investigations.

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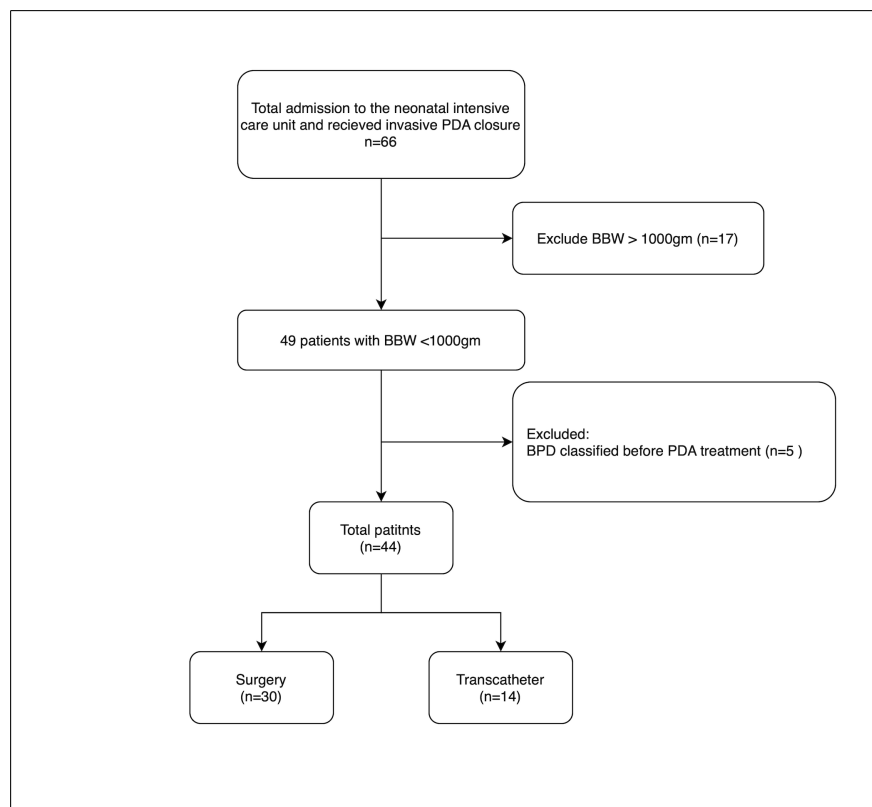
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