# Mandatory Closure Versus Nonintervention for Patent Ductus Arteriosus in Very Preterm Infants

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**Objective** To determine whether a nonintervention approach for treating hemodynamically significant patent ductus arteriosus (PDA) is associated with decreased mortality and/or morbidity compared with a mandatory closure approach in extremely low birth weight infants.

**Study design** We reviewed the medical records of 178 infants of 23-26 weeks' gestational age with PDA, requiring ventilator treatment, and with hemodynamically significant PDA ≥2 mm in size. Mandatory closure was used during period I (July 2009 to December 2011, n = 81), and nonintervention was used during period II (January 2012 to June 2014, n = 97).

**Results** During period I, 64% of infants were first treated with indomethacin, and 82% were ultimately ligated surgically. During period II, no infant was treated with indomethacin and/or ligation. The average postnatal day of PDA closure was day 13 and day 44 during periods I and II, respectively. There was significantly more use of diuretics and fluid restriction during period II compared with period I. There was no difference in mortality or morbidities such as necrotizing enterocolitis or intraventricular hemorrhage. The incidence of bronchopulmonary dysplasia (BPD) and the propensity score adjusted OR of BPD were significantly lower during period II compared with period I.

**Conclusions** Despite longer PDA exposure, nonintervention was associated with significantly less BPD compared with mandatory closure. Additional study is warranted to determine the benefits and risks of non-intervention for the hemodynamically significant PDA in extremely low birth weight infants. *(J Pediatr 2016;177:66-71).*

Patent ductus arteriosus (PDA) in preterm infants is associated with increased mortality and morbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH)[1]; however, a causal relationship has not been established. Although it is traditional to manage PDA with cyclooxygenase inhibitors and/or surgical ligation, definite evidence supporting the benefit of these PDA therapies over watchful waiting with supportive care is lacking,[2-4] and they might be associated with adverse effects on multiple organ systems.[5,6] There are emerging concerns about morbidity associated with surgical ligation, especially in the most immature babies and in the first week of life.[7-9] The question of whether mandatory PDA closure therapy is more beneficial than conservative nonintervention that allows spontaneous closure remains unanswered.[2,3,10]

The paucity of published data regarding supportive care of PDA[4,11-13] has created challenges in generating rational, evidence-based management of PDAs in very premature infants. In our neonatal intensive care unit (NICU), the policy for management of a hemodynamically significant patent ductus arteriosus (HS-PDA) in extremely preterm infants with gestational age (GA) of 23-26 weeks has evolved as follows: between July 2009 and December 2011 (period I), a mandatory PDA closure approach via indomethacin and/or surgical ligation was conducted. Surgical ligation was performed as primary treatment when the indomethacin was contraindicated and as secondary treatment when indomethacin treatment failed. From January 2012 to June 2014 (period II), the PDA management strategy changed to a nonintervention approach without targeted pharmacologic or surgical treatment regardless of the hemodynamic significance. The change was prompted by literature review, the increasing concerns about the risks of early surgical ligation, and the observation that less-invasive treatment appeared to be tolerated in preterm infants <27 weeks of age who did not require early ventilator support.[4,11-13] In the present retrospective observational study, we reviewed the medical records of preterm infants of 23-26 weeks' gestation with HS-PDA to determine whether

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| BPD | Bronchopulmonary dysplasia |
| ELBW | Extremely low birth weight |
| GA | Gestational age |
| HS-PDA | Hemodynamically significant patent ductus arteriosus |
| IVH | Intraventricular hemorrhage |
| NEC | Necrotizing enterocolitis |
| NICU | Neonatal intensive care unit |
| PDA | Patent ductus arteriosus |
| PRN | Pro re nata |
| SMC | Samsung Medical Center |

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our change from a mandatory closure to a nonintervention approach was associated with improved or worsened adverse outcomes in the most immature infants.

## Methods

Data collection was approved by the Institutional Review Board of Samsung Medical Center (SMC), which allowed a waiver of informed consent for this retrospective chart review (IRB No. SMC 2013-02-129). The medical records of 178 of 250 preterm infants with GA of 23-26 weeks born and admitted to the SMC NICU and presenting with HS-PDA were reviewed retrospectively. The details of 72 infants excluded from analysis are shown in **Figure 1** (available at www.jpeds.com).

After admission to the NICU, infants were examined daily in the first 2 weeks for changes in respiratory support and clinical symptoms/signs related to HS-PDA, including deterioration in respiratory condition, cardiac murmur, hyperactive precordium, hypotension, and widened pulse pressure. If any of these were found, a 2-dimensional echocardiogram (ACUSON Sequoia C512; Siemens Medical Solutions, Mountain View, California) was performed within 48 hours. If dominant left-to-right flow (by gain-optimized color Doppler) through a PDA 2 mm or more in size was found, these symptoms and signs could be regarded as due to symptomatic PDA. However, we did not treat extubated infants regardless of PDA size on echocardiography throughout the study period.

During the study period, 2 distinctly different approaches were used for the management of HS-PDA, with no changes in strategies for respiratory support for extremely low birth weight (ELBW) infants. In period I (July 1, 2009, to December 31, 2011, n = 81), all ELBW infants with HS-PDA, defined as ≥2 mm with predominant left-to-right shunt by echocardiography, and receiving ventilator support with symptoms/signs suggestive of PDA had mandatory PDA closure. Mandatory closure was initiated with intravenous indomethacin treatment (0.2 mg/kg for the initial dose and 2 subsequent doses of 0.2 mg/kg/dose every 12 hours), usually at the end of the first week to avoid unnecessary drug exposure, as a 30% spontaneous closure rate at postnatal day 7 has been reported, even in infants with birth weight <1000 g.[14] Early surgical ligation was performed as soon as possible if the PDA failed to close with 1 or 2 cycles of intravenous indomethacin, or if indomethacin treatment was contraindicated. The decision for the ligation was made by the attending neonatologists, based on clinical judgment that medical therapy had failed or a contraindication for indomethacin treatment existed. Ligation did not depend on strict echocardiographic criteria, except for PDA size (≥2 mm).

In period II (January 1, 2012 to June 30, 2014, n = 97), we changed our treatment strategy to a nonintervention approach. Infants were first managed with judicious fluid restriction and pro re nata (PRN) diuretics with respiratory support as needed. Treatment with indomethacin or ligation was reserved as a last resort, and no infant with HS-PDA received either therapy during period II.

Among infants who had a smaller PDA size (<2 mm) or who did not require ventilator support within the first 2 weeks of life, 2 infants received later indomethacin treatment in the third and fourth week of life. Both infants experienced a sudden deterioration of respiratory condition, including reintubation after previous weaning from the ventilator, and simultaneously increased PDA size to more than 2 mm. They ultimately had PDA closure within 2 weeks after indomethacin treatment.

Clinical characteristics including GA, birth weight, Apgar scores at 1 and 5 minutes, sex, small for gestational age, mode of delivery, chorioamnionitis, pulmonary hemorrhage, and antenatal steroid use, days of nasogastric feeding, and data on weight z score at discharge were analyzed. GA was determined by maternal last menstrual period and the modified Ballard test. Small for gestational age was defined when birth weight was less than the tenth percentile. Chorioamnionitis was confirmed by placental pathology. Pulmonary hemorrhage was defined as presenting with bloody fluid from the endotracheal tube plus radiologic suggestion of pulmonary hemorrhage developing within the first week of life. Oliguric renal failure was defined as urine output of less than 0.5 mL/kg/day for ≥24 hours combined with a serum creatinine level of 2.0 mg/dL or greater. Nonoliguric renal dysfunction was defined as a serum creatinine level of 2.0 mg/dL or greater without oliguria. Diuretic use was defined as use of diuretics for at least 3 days during the first 2 weeks of life. Maximum levels of blood urea nitrogen and serum creatinine during the first 2 weeks of life were compared between periods. Use of inotropic drugs was defined as use of dopamine and/or dobutamine for ≥24 hours within the first 2 weeks of life.

Outcome measures included death before discharge, BPD, defined as the need for supplemental oxygen and/or positive pressure to maintain oxygen saturation >90% at 36 weeks' gestation,[15] IVH (grade ≥3),[16] periventricular leukomalacia, NEC (>Bell stage IIb),[17] and retinopathy of prematurity (stage ≥3).[18] Duration of invasive mechanical ventilation, continuous positive airway pressure, and supplemental oxygen therapy (low flow nasal cannula) were recorded. The data for long-term neurodevelopmental outcome were not collected in this study.

To demonstrate the natural time course of HS-PDA according to differences in management, the cumulative incidence rates of ductal patency were analyzed during periods I and II. A propensity score-adjusted regression model was used to calculate aORs for mortality, BPD, and composite BPD or death in period II vs period I with 95% CIs.

### Statistical Analyses

Statistical differences between the study periods were calculated with $\chi^2$ tests for categorical variables and a *t* test or Mann-Whitney *U* test for quantitative variables. For the propensity score-adjusted regression model, logistic regression adjusted for propensity score was used as a covariate. The cumulative incidence rates of ductal patency were analyzed with the Kaplan-Meier estimation, and differences between the 2 periods were analyzed by Cox proportional-hazards regression. Propensity score included GA, birth weight, male, small for gestational age, use of antenatal steroids, and Apgar score at 5 minutes.