# 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;■■:■■-■■).*

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

| | |
|---|---|
| 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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Supported by the Samsung Medical Center (20 by 20 Project, Best #3, GFO1150091).


http://dx.doi.org10.1016/j.jpeds.2016.06.046

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.



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A *P* value of <.05 was considered statistically significant. Statistical analysis was executed with SAS version 9.4 (SAS Institute, Cary, North Carolina) and R 3.0.3 (Vienna, Austria; http://www.R-project.org/).

## Results

Table I shows demographic and clinical findings of infants with HS-PDA during periods I and II. The use of inotropic drugs for ≥24 hours within the first 2 weeks of life was significantly lower during period II compared with period I. Increased use of inotropic drugs during period I compared with period II was attributed to postoperative myocardial dysfunction (5 infants in period I vs 0 infants in period II). Other variables, including GA, were not significantly different between the study periods.

### Treatment of HS-PDA

During period I, 52 (64%) of a total of 81 infants with HS-PDA received intravenous indomethacin at an average postnatal day of 7. Only 15 of 52 (29%) infants responded to pharmacologic treatment, and the remaining 37 of 52 (71%) infants received surgical ligation due to failure of pharmacologic treatment. Because of contraindications to pharmacologic treatment, 29 of 81 (36%) infants were treated with surgical ligation only. A total of 66 of 81(82%) infants ultimately received surgical ligation (Table I and Figure 1). During period II, the age of diagnosis was slightly but significantly delayed compared with period I (6.4 vs 5.6 days), and the size of HS-PDA was similar. All infants were managed only with fluid restriction, and no infants received indomethacin or ligation treatment.

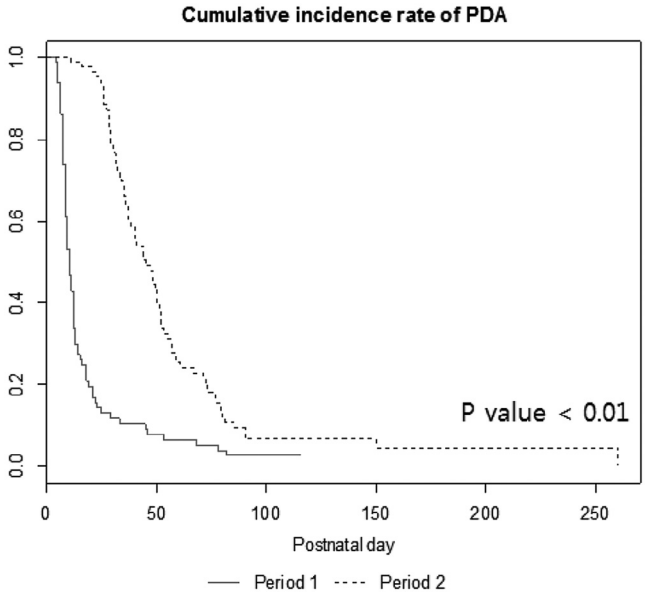


**Figure 2.** Cumulative incidence rate of ductal patency during hospitalization in infants with initial HS-PDA according to study period.

**Table I. Clinical characteristics of infants with HS-PDA during periods I and II**

| | Total (n = 178) | |
|---|---|---|
| | Period I (n = 81) | Period II (n = 97) |
| Baseline demographics | | |
| GA, wk | 24.6 ± 1.1 | 24.5 ± 1.0 |
| Birth weight, g | 728 ± 134 | 718 ± 137 |
| Male, n (%) | 35 (43) | 54 (56) |
| Small for gestational age, n (%) | 8 (10) | 8 (8) |
| Cesarean delivery, n (%) | 68 (84) | 76 (78) |
| Antenatal steroids, n (%) | 69 (85) | 79 (81) |
| Chorioamnionitis, n (%) | 50 (63) | 56 (58) |
| Apgar score, 1 min | 4.7 ± 1.5 | 4.5 ± 1.4 |
| Apgar score, 5 min | 7.2 ± 1.4 | 6.9 ± 1.4 |
| Pulmonary hemorrhage during first week, n (%) | 5 (6) | 2 (2) |
| Use of inotropic drugs, n (%) | 20 (25) | 16 (16)* |
| First enteral feeding, d | 1 ± 1 | 1 ± 1 |
| Full enteral feeding (>120 mL/kg/day), d | 58 ± 28 | 57 ± 34 |
| Body weight at discharge (z score) | −5.9 ± 0.7 | −5.8 ± 1.1 |
| Body weight at corrected age of 12 mo (z score) | −1.7 ± 0.9 | −1.9 ± 1.0 |
| Burden and treatment of HS-PDA | | |
| Age at first diagnosis, d | 5.6 ± 1.8 | 6.4 ± 2.3* |
| PDA size at diagnosis, mm (min-max) | 2.6 ± 0.5 (2.0 - 3.8) | 2.5 ± 0.5 (2.0 - 4.2) |
| Age of PDA closure, d | 12.9 ± 12.3 | 44.3 ± 30.1* |
| PDA open until discharge, n (%) | 1 (1) | 5 (5) |
| Indomethacin, n (%) | 52 (64) | |
| Indomethacin ≥2 cycles, n (%) | 2 (3) | |
| Age at first indomethacin, d | 7 ± 5 | |
| Surgical ligation, n (%) | 66 (82) | |
| Age at ligation, d | 12 ± 7 | |

*$P < .05$ compared with period I.

### Fate of HS-PDA

The postnatal age of PDA closure during hospitalization was markedly delayed during period II compared with period I (44.2 vs 12.9 days; Table I and Figure 2). During period I, 1 infant did not experience PDA closure after receiving indomethacin treatment but was weaned from the ventilator and stabilized without further indomethacin treatment. During period II, 5 infants (5%) were discharged without PDA closure. On follow-up, 3 of 5 infants during period II had spontaneous ductus closure by echocardiography done at 4, 5, and 9 months of postnatal age. In the remaining infants, the PDA was closed by transcatheter occlusion at 10, 12, and 13 months of age, respectively.

### Fluid Intake, Energy Intake, and Renal Function

Energy intake and renal function were similar between the 2 study periods. Fluid intake at postnatal days 14 and 21 was significantly lower, and the use of diuretics within the first 2 weeks was significantly greater during period II compared with period I (**Table II;** available at www.jpeds.com).



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**Table III. Adverse outcomes of infants with HS-PDA during periods I and II**

| | Total (n = 178) | |
|---|---|---|
| | Period I (n = 81) | Period II (n = 97) |
| Mortality during hospitalization, n (%) | 9 (11) | 9 (9) |
| IVH (≥ grade 3), n (%) | 15 (19) | 12 (12) |
| Cystic periventricular leukomalacia, n (%) | 12 (15) | 15 (16) |
| ROP (≥ stage 3), n (%) | 5 (6) | 7 (7) |
| NEC (≥ stage IIb), n (%) | 10 (13) | 12 (12) |
| NEC perforation, n (%) | 8 (10) | 8 (8) |
| Spontaneous intestinal perforation, n (%) | 2 (3) | 2 (2) |
| Sepsis, n (%) | 18 (22) | 28 (29) |
| Respiratory outcome | | |
| BPD, n (%) | 46 (58) | 35 (38)* |
| Duration of invasive mechanical ventilation | 32 ± 23 | 38 ± 22 |
| Duration of HFOV | 19 ± 15 | 24 ± 17* |
| Duration of NCPAP | 41 ± 22 | 34 ± 20* |
| Duration of supplemental oxygen | 12 ± 17 | 6 ± 18* |
| Discharge with home oxygen, n (%) | 10 (12) | 7 (7) |

*HFOV*, high-frequency oscillatory ventilation; *NCPAP*, nasal continuous positive airway pressure; *ROP*, retinopathy of prematurity.
*$P < .05$ compared with period I.

### Adverse Outcomes

During period II, the incidence of BPD, defined as requiring supplemental oxygen and/or positive pressure to maintain oxygen saturation >90% at 36 weeks' gestation, duration of nasal continuous positive airway pressure, and supplemental oxygen were significantly lower compared with period I (**Table III**). The incidence of other adverse outcomes, including mortality, IVH (grade 3 and 4), cystic periventricular leukomalacia, retinopathy of prematurity (stage ≥3), and NEC (stage ≥IIb), were not significantly different between the study periods.

### Propensity Score aORs

The propensity score aORs of the nonintervention approach during period II over the mandatory closure approach during period I were aOR 0.8 (95% CI 0.3-2.2) for mortality, aOR 0.4 (95% CI 0.2-0.8) for BPD, and aOR 0.5 (95% CI 0.2-0.9) for composite BPD or mortality in infants with HS-PDA. Although the OR for mortality (OR 0.8, 95% CI 0.3~2.2) was not significantly different, the ORs of the nonintervention approach during period II for BPD (OR 0.4, 95% CI 0.2~0.8) and composite BPD or mortality (OR 0.5, 95% CI 0.2~0.9) were significantly lower compared with the mandatory closure approach during period I.

## Discussion

Appropriate management of the HS-PDA, especially in very premature infants, is an ongoing challenge. Recent comprehensive reviews have not provided definite evidence that early traditional PDA treatments have greater benefit for premature infants compared with alternative supportive strategies such as fluid restriction.[2,3,10] Furthermore, some studies suggest that reduced ligation might improve PDA outcomes.[19-21] In the present retrospective observational study, all ELBW infants with HS-PDA, defined as ≥2 mm and receiving ventilator support, were treated actively with indomethacin and/or ligation via a mandatory PDA closure approach during period I. During period II, we observed that spontaneous but later closure of HS-PDA was achieved in most infants with a nonintervention approach consisting of fluid restriction and PRN diuretics without indomethacin or ligation. Despite later PDA closure, nonintervention was not associated with increased mortality or morbidities such as NEC or IVH, and the incidence of BPD was significantly reduced compared with mandatory closure. These findings suggest that nonintervention might be a reasonable alternative to mandatory closure in extremely preterm infants with HS-PDA. Our findings also support the need for future prospective randomized trials to reexamine the pros and cons of different approaches to HS-PDA treatment in very preterm infants.

The lack of a standardized method to diagnose HS-PDA makes its clinical impact and contribution to preterm morbidities difficult to define. In this study, the PDA diameter and the need for the invasive ventilator support were used to determine whether to treat a PDA with indomethacin and/or ligation during period I. During period II, however, spontaneous closure of HS-PDAs was achieved in 95% of infants with the nonintervention approach without increases in mortality or morbidities. The development of new diagnostic tools, including clinical, biochemical, and echocardiographic findings,[9,22] is necessary to better identify infants with HS-PDA requiring specific treatment.[5,23,24]

During period I, indomethacin was begun on day 7 to avoid unnecessary drug exposure.[14] Only 29% of these infants responded to indomethacin treatment, and the rest were treated with ligation. When we included those initially treated surgically, 82% of infants receiving the mandatory PDA closure approach were surgically ligated. Similar to our data, Dani et al[25] reported that infants with GA of 23-25 weeks had a high risk of developing PDA refractory to ibuprofen treatment, and Jhaveri et al[19] reported that 81% of infants at 24-25 weeks' gestation ultimately were treated with surgical ligation. Our indomethacin failure rate and the resultant high surgical ligation rate might be attributable to the younger GA population in this study.[19,25] Thus, our study also compared the therapeutic efficacy of "ultimate surgical ligation" vs "no treatment" in extremely preterm infants of 23-26 weeks' gestation with HS-PDA.

Few studies have reported the natural history of PDA in extremely preterm infants. Rolland et al[26] observed a spontaneous PDA closure rate of 60% in infants of 24-25 weeks' gestation at an average of 61 postnatal days. Herrman et al[11] reported that 86% (18/21) of very low birth weight infants with a persistent PDA at discharge were spontaneously closed at 48 weeks' gestation, with 2 infants undergoing coil occlusion at 11 months of age. In the present study, we were more stringent in the use of indomethacin and/or ligation with the nonintervention approach during period II compared with other conservative PDA treatment studies,[4,11-13,19-21] and no infants during period II were treated with indomethacin and/or ligation. Spontaneous closure occurred at a mean age of 44 ± 30.1 days, with 5 (5%) infants discharged with persistent PDA. Of these, 2 (2%) infants



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required coil occlusion after discharge. Our findings suggest that nonintervention might be equally effective in very preterm infants with HS-PDA.

Besides "watchful waiting," the nonintervention approach for HS-PDA included fluid restriction and the use of intermittent diuretics. High fluid intake of >170 mL/kg/day has been associated with an increased risk of neonatal morbidities such as persistent PDA,[27,28] driving the use of high humidified incubators to decrease total fluid intake during the first week of life in ELBW infants.[29] Our data indicate that even lower fluid intakes of ≤107 mL/kg/day during the first week of life could be achieved without restricting caloric intake (**Table II**) and without electrolyte or renal disturbances.[30] Replication of our results with a nonintervention approach might depend on similar fluid intake goals for the first 3 weeks of life (**Table II**). We also observed more use of inotropic drugs during period I, given for postoperative myocardial dysfunction and possibly indicating a higher rate of PDA treatment complications after surgical ligation.

Later closure of HS-PDA with prolonged left-to-right ductal shunt in very preterm infants might increase the risk of morbidities such as NEC, IVH, and BPD.[4,31-34] Even though PDA closure occurred at a much later postnatal age after nonintervention, there were no significant differences in mortality and morbidities such as NEC and IVH (≥3), and a significantly lower incidence of BPD was observed. Although pharmacologic closure improved pulmonary mechanics and increased alveolar growth in premature baboons with a persistent PDA,[35] these beneficial effects were abolished with surgical ligation.[8,36] Taken together, these findings raise the possibility that the detrimental effects of surgical ligation might outweigh the benefit derived from PDA closure.[37] Thus, surgical ligation might directly contribute to the development of BPD what it is intended to prevent.[5,38,39] The more prolonged use of high-frequency oscillatory ventilation during period II also may have contributed to the lower incidence of BPD.[40]

A prospective, randomized clinical trial of pharmacologic vs no treatment could answer whether more prolonged exposure to HS-PDA leads to BPD or other morbidities in very preterm infants. Our data showing the favorable outcome of nonintervention lends support to the safety and possible efficacy of a "no treatment" control group. We are thus conducting a prospective, double-blind randomized controlled trial comparing the therapeutic efficacy of "exclusive pharmacologic treatment with oral ibuprofen" vs "placebo" therapy (ClinicalTrials.gov ID, NCT02128191).

The limitations of the present study include the single-center, retrospective, and noncontrolled observational study design, as well as arbitrary criteria for HS-PDA defined only by PDA size and ventilator dependency. Variations in clinical management policies during periods I and II, including respiratory management, fluid administration, and use of diuretics might be other confounding variables. We also acknowledge the lack of long-term neurodevelopmental outcome data. Future prospective double blind trials will clarify these issues. We also suggest the need to develop robust definitions of echocardiographically significant PDA as well as improved pharmacologic approaches.

In conclusion, although closure of a HS-PDA was more delayed, a nonintervention approach of judicious fluid restriction and PRN use of diuretics without indomethacin and/or ligation was not associated with increased mortality or morbidities such as NEC or IVH (≥3). Nonintervention was also associated with significantly less BPD compared with mandatory closure. These findings warrant a future, prospective, randomized study to determine the short and long-term benefits and risks of nonintervention for HS-PDA in very preterm infants. ■

Submitted for publication Feb 3, 2016; last revision received Apr 26, 2016; accepted Jun 13, 2016

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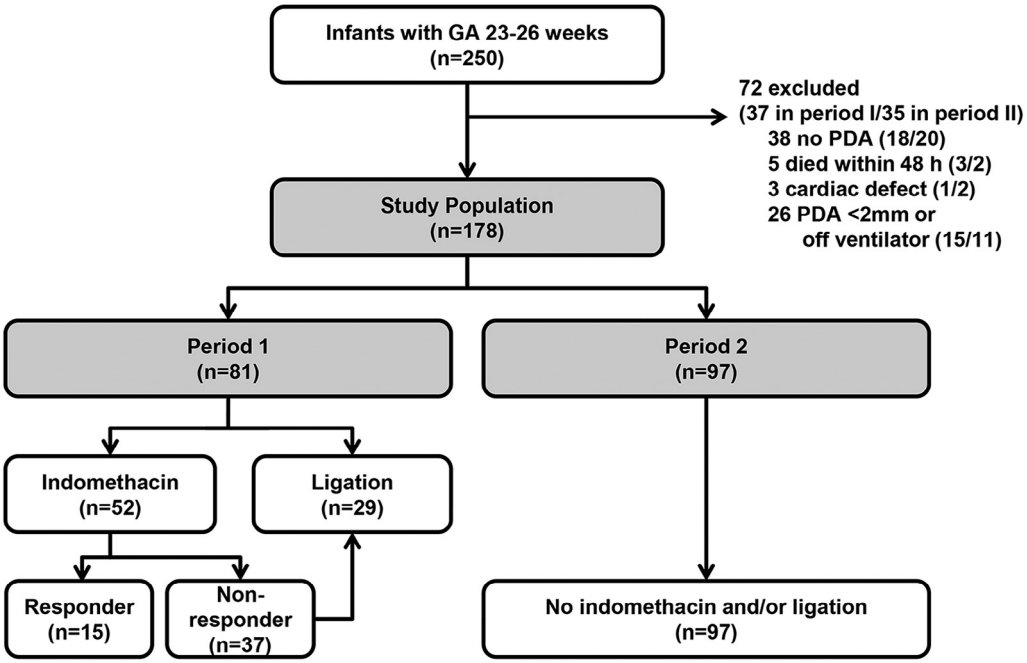


**Figure 1.** Study population.

**Table II. Fluid intake, energy intake, and renal function in infants with HSPDA during periods I and II**

| | Total (n = 178) | |
|---|---|---|
| | Period I (n = 81) | Period II (n = 97) |
| Fluid intake, mL/kg/d | | |
| DOL 7 | 106 ± 21 | 107 ± 20 |
| DOL 14 | 117 ± 21 | 101 ± 23* |
| DOL 21 | 125 ± 22 | 107 ± 25* |
| DOL 28 | 120 ± 26 | 115 ± 21 |
| Energy intake, kcal/kg/d | | |
| DOL 7 | 68 ± 18 | 70 ± 18 |
| DOL 14 | 81 ± 20 | 77 ± 18 |
| DOL 21 | 86 ± 21 | 83 ± 19 |
| DOL 28 | 85 ± 20 | 87 ± 18 |
| Renal function | | |
| Oliguric renal failure, n (%) | 12 (15) | 13 (13) |
| Nonoliguric renal dysfunction | 12 (15) | 21 (22) |
| Use of diuretic drugs, days | 1.6 ± 1.4 | 2.1 ± 1.9* |
| Peak blood urea nitrogen level, mg/dL | 33 ± 13 | 33 ± 11 |
| Peak serum creatinine level, mg/dL | 1.4 ± 0.5 | 1.4 ± 0.5 |

*DOL*, day of life.
*$P < .05$ compared with period I.



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