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Timing of surgical ligation and morbidities in very low birth weight infants

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Abstract

The present study examined whether early patent ductus arteriosus (PDA) surgical ligation at ≤2 weeks of life was associated with increased morbidities and mortality in very low birth weight infants (VLBWIs) who were diagnosed with hemodynamically significant (hs) PDA. Between December 2013 and December 2015, a total of 407 VLBWIs were admitted, of whom 145 (35.6%) infants were diagnosed with an hs PDA. The clinical data for these infants were retrospectively collected for analysis. Among the 145 VLBWIs with an hs PDA, 58 (40%) infants had surgical ligation for PDA; of these, 29 (50%) infants had early ligation (EL; ligation at ≤2 weeks of life) and 29 (50%) infants had late ligation (LL; ligation at ≥2 weeks of life). The mean gestational age and birth weight were significantly lower in the PDA-ligated group compared with the nonligated group. In addition, pulmonary hypertension at ≤1 week of life and neonatal seizures were significantly more prevalent in the ligated group ($P < 0.05$). Increased rate of ROP laser treatment, bronchopulmonary dysplasia, longer hospital stays, and longer duration of mechanical ventilation were found in ligated group ($P < 0.05$). However, the morbidities and mortality did not differ significantly between the EL and LL groups. Pulmonary hypertension at ≤1 week of life was significantly associated with LL ($P = 0.019$), which was consistently a risk factor for hs PDA ligation in our multivariable logistic regression analysis. EL was not significantly associated with increased hospital morbidities and mortality in VLBWIs with hs PDA. Pulmonary hypertension at ≤1 week of life can be a risk factor for the need for surgical ligation of hs PDA.

Abbreviations: ARF = acute renal failure, BPD = bronchopulmonary dysplasia, EL = early ligation, Hs = hemodynamically significant, IVH = intraventricular hemorrhage, LL = late ligation, NEC = necrotizing enterocolitis, NICU = neonatal intensive care unit, PDA = patent ductus arteriosus, ROP = retinopathy of prematurity, TPN = total parental nutrition, VLBWI = very low birth weight infants.

Keywords: ligation, morbidity, mortality, patent ductus arteriosus, pulmonary hypertension

1. Introduction

The incidence of patent ductus arteriosus (PDA) among very low birth weight infants (VLBWIs) is reported to be 30%.[1] Its incidence is inversely related to gestational age; depending on which diagnostic criteria is used, PDA is estimated to affect up to 80% of infants born at 24–25 weeks gestation.[2] Despite the higher incidence of PDA among extremely premature infants, examining hemodynamically significant (hs) PDA is an important factor in the assessment of clinical outcomes of VLBWIs. To standardize the definition of hs PDA before the study, we applied the comprehensive McNamara and Sehgal[3] criteria of PDA to infants in our neonatal intensive care unit (NICU) beginning in 2012. This criterion is based on a combination of clinical and echocardiographic findings and is staged from mild to severe. Without intervention, severe and prolonged hs PDA in premature infants has been shown to increase morbidities such as intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), kidney injury, heart failure, and bronchopulmonary dysplasia (BPD).[4–8] Therefore, identifying and closely monitoring hs PDA in VLBWIs are important measures to help prevent adverse outcomes. In addition, early surgical ligation has been advocated as the optimal therapy for PDA to ensure definitive ductal closure with minimal morbidity and mortality risk.[9]

The aim of the present study was to evaluate whether EL (ligation at ≤2 weeks of life) was associated with increased or decreased morbidities and mortality when compared to late ligation (ligation at ≥2 weeks of life) in VLBWIs. In addition, risk factors for surgical ligation of PDA were analyzed.

2. Materials and methods

Between December 2013 and December 2015, of the 407 VLBWIs admitted to our NICU at Seoul St. Mary's Hospital, 145 (35.6%) were diagnosed with hs PDA. The clinical data for these infants relating to hs PDA, hospital morbidities, and mortality were retrospectively collected for analysis. VLBWIs were screened for PDA within the first 4 days of life, and their diagnoses were confirmed with a 2-dimensional echocardiogram.

If hs PDA was found in the first week of assessment, serial echocardiogram and close monitoring were continued weekly

Editor: Bernhard Resch.

YY wrote the first draft of the manuscript, and no honorarium, grant, or other form of payment was received to produce this manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. This manuscript is not under simultaneous consideration with another journal.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:14(e6557)

Received: 19 December 2016 / Received in final form: 9 March 2017 / Accepted: 11 March 2017

http://dx.doi.org/10.1097/MD.0000000000006557

until the hs PDA was resolved. Persistent hs moderate-stage PDA (stage C3 based on the criteria developed by McNamara and Sehgal[3]) were treated either pharmacologically with oral ibuprofen or with surgical ligation. Clinical hs moderate-stage PDA were VLBWIs who manifested clinical symptoms such as oxygenation difficulty, frequent (hourly) apneas with increasing ventilation requirements, inability to advance feeding, systemic hypotension, mild metabolic acidosis, and cardiomegaly on radiography. VLBWIs with complex congenital heart disease were excluded from this study. No infant received prophylactic treatment for PDA. Throughout the study, oral ibuprofen was prescribed at an initial dose of 10 mg/kg and followed by 2 additional doses of 5 mg/kg on consecutive days.[10,11] Surgical ligation of PDA was performed on VLBWIs who could not be treated pharmacologically, due to various clinical contraindications (acute renal failure [ARF], positive DIC with bleeding tendency, etc.), or because pharmacological interventions had previously failed. Surgical PDA ligation was routinely performed at the patient's bedside in the NICU, and all ligations were performed by an experienced pediatric cardiothoracic surgeon using a metal clip through the third or fourth intercostal space after posterolateral thoracotomy. The study was approved by the Ethics Committee of Seoul St. Mary's Hospital, The Catholic University of Seoul, Korea.

2.1. Definitions

EL was defined as the surgical ligation of a PDA at ≤2 weeks of life, and late ligation (LL) was defined as the surgical ligation of a PDA at ≥2 weeks of life.

Patients with hs PDA were defined as those who met the clinical and echocardiographic criteria proposed by McNamara and Sehgal[3] for at least a moderate stage (stage ≥3) hs PDA. Medical response was defined as a reduction of the size of the PDA to less than 1.5 mm and an improvement in both clinical and echocardiographic criteria (stage ≤2). Medical failure was defined as a persistent hs PDA (stage ≥3) with a ductal size greater than 1.5 mm following 2 courses of oral ibuprofen, or any cases in which a second course of oral ibuprofen was unable to be used due to ARF, NEC, or DIC.

Pulmonary hypertension was defined if nitric oxide, sildenafil, or iloprost was used at ≤1 week of life. BPD was diagnosed if oxygen use exceeding 0.21 was still needed at a corrected gestational age of 36 weeks. NEC was diagnosed for those cases that met the criteria for grade II or higher using Bell staging criteria for NEC. IVH > grade II was defined as active bleeding in the ventricles, and the grade designation was based on Drs Papile and Levene classification criteria. Retinopathy of prematurity (ROP) was defined and classified according to the International Classification of Diseases for ROP. In this study, the morbidities were described as following: IVH > grade II, neonatal seizure, sepsis, NEC operation, ROP laser treatment, BPD, total parental nutrition (TPN), days of mechanical ventilation, hospitalized days, and periventricular leukomalacia.

2.2. Statistical analysis

Continuous variables were compared using Student *t* test and are expressed as the means ± standard deviations. Discrete variables were compared using a χ^2 test or a Fisher exact test and are expressed as percentages. Expired patients were excluded in TPN, mechanical ventilation, and hospitalized days. They were expressed as median, interquartile range, and Mann–Whitney *U* test was used to find the *P* value. All analyses were 2-tailed, and statistical significance was defined as a *P* value lower than 0.05. A multivariate logistic regression model was used to assess for any confounding risk factors for surgical ligation of PDA. Odds ratios and 95% confidence intervals were calculated using a multivariate statistical model that included the following predictors related to surgical ligation of PDA with a stepwise logistic regression analysis: gestational age, birth weight, pulmonary hypertension, and neonatal seizures. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS-PC Inc., Chicago, IL).

3. Results

3.1. Demographic data

Of the 407 VLBWIs admitted to our NICU between December 2013 and December 2015, 145 (35.6%) infants were diagnosed with an hs PDA.

Of the 145 VLBW infants with hs PDA, 58 (40%) infants underwent surgical ligation for PDA—29 (50%) infants underwent EL and 29 (50%) infants underwent LL. Among the 58 ligated infants, 27 (46.6%) infants underwent surgical ligation after oral ibuprofen failed to close the hs PDA (Table 1).

Among the VLBWIs with an hs PDA, the mean gestational age and birth weight were significantly lower in the PDA-ligated group compared with the nonligated group (27.3 ± 2.2 vs 28.7 ± 2.5, 1043 ± 270 vs 1194 ± 29, $P = 0.001$). In addition, pulmonary hypertension at ≤1 week of life and neonatal seizures were significantly associated with the ligated group ($P < 0.05$). Morbidities were significantly higher in the ligated group, including an increased rate of ROP laser treatment, increased duration of hospital stay, and mechanical ventilation ($P < 0.05$).

Table 1

Clinical characteristics of VLBWIs (n = 145) with PDA.

	No surgical ligation (n = 87)	Surgical ligation group (n = 58)	*P*
Gestational age, wk	28.7 ± 2.5	27.3 ± 2.2	0.001
Birth weight, g	1194 ± 291	1043 ± 270	0.001
Male (n [%])	38 (43.7)	26 (44.8)	0.891
Resuscitation at birth	18 (20.7)	23 (39.1)	0.058
RDS	80 (92.0)	54 (94.7)	0.521
Surfactant use ≥2 times	21 (24.1)	16 (27.5)	0.346
Pulmonary hemorrhage	10 (11.5)	11 (19.0)	0.210
Pulmonary hypertension*	10 (11.5)	16 (37.6)	0.013
Oral ibuprofen use	56 (64.4)	27 (46.6)	0.034
IVH > grade II	17 (19.5)	14 (24.1)	0.053
Neonatal seizure	14 (16.1)	20 (34.5)	0.010
Sepsis	46 (52.9)	36 (62.1)	0.274
NEC operation	4 (4.7)	8 (14.0)	0.065
ROP laser treatment	12 (13.8)	17 (29.3)	0.022
BPD	42 (48.3)	46 (79.3)	<0.001
TPN, d†	50 (18, 75)	52 (34.75, 74.5)	0.591
Mechanical ventilation, d†	9 (2, 48)	30 (14, 56.5)	<0.001
Hospitalized, d†	48 (24, 65)	72 (52, 97)	<0.001
PVL	19 (21.8)	15 (26.3)	0.543
Mortality	13 (14.9)	13 (22.4)	0.251

BPD = bronchopulmonary dysplasia, g = gram body weight, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, PVL = periventricular leukomalacia, RDS = respiratory distress syndrome, ROP = retinopathy of prematurity, TPN = total parental nutrition, VLBWI = very low birth weight infant.

* Use of nitric oxide, sildenafil, or iloprost within 1 week of birth.

† Mann–Whitney *U* test was used, and expired patients were excluded.

Table 2

Clinical characteristics of VLBWIs with PDA ligation (n = 58).

	Early surgical ligation (n = 29)	Late surgical ligation group (n = 29)	*P*
Gestational age, wk	27.4 ± 2.6	27.2 ± 1.8	0.770
Birth weight, g	1017 ± 294	1069 ± 247	0.464
Male (n [%])	13 (44.8)	13 (44.8)	1.000
Resuscitation at birth	29 (100)	29 (100)	1.000
RDS	29 (100)	25 (89.3)	0.070
Surfactant use ≥2 times	11 (37.9)	5 (17.2)	
Pulmonary hemorrhage	5 (17.2)	6 (20.7)	0.738
Pulmonary hypertension*	4 (13.8)	12 (41.4)	0.019
Oral ibuprofen use	11 (37.9)	16 (55.2)	0.188
Age at surgery, d	9.2 ± 3.4	30.8 ± 28.3	<0.001
IVH > grade II	12 (41.4)	8 (27.6)	0.269
Neonatal seizure	11 (37.9)	9 (31.0)	0.581
Sepsis	21 (72.4)	15 (51.7)	0.104
NEC operation	4 (13.8)	4 (13.8)	1.000
ROP laser treatment	8 (27.6)	9 (31.0)	0.773
BPD	22 (75.9)	24 (82.8)	0.517
TPN, d†	64 (40, 82)	46 (30.0, 54.5)	0.061
Mechanical ventilation, d†	36 (21.25, 58.75)	21 (13.25, 51.75)	0.228
Hospitalized, d†	76 (48, 97)	70.5 (52.75, 98.0)	0.798
PVL	9 (31.0)	6 (21.4)	0.410
Mortality	5 (17.2)	8 (27.6)	0.345

BPD = bronchopulmonary dysplasia, g = gram body weight, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, PVL = periventricular leukomalacia, RDS = respiratory distress syndrome, ROP = retinopathy of prematurity, TPN = total parental nutrition, VLBWI = very low birth weight infant.

* Use of nitroxide, sildenafil, or iloprost within 1 week of birth.

† Mann–Whitney *U* test was used, and expired patients were excluded.

Table 3

Risk factor for hs PDA surgical ligation in a multiple logistic regression analysis*.

	OR	*P*	95% CI
Gestational age, wk	0.839	0.125	0.670–10.50
Birth weight, g	1.000	0.761	0.998–1.002
Pulmonary hypertension†	2.164	0.016	0.827–5.662
IVH > grade II	0.981	0.967	0.400–2.407
Neonatal seizure	1.993	0.114	4.683

CI = confidence interval, IVH = intraventricular hemorrhage, OR = odds ratio.

* Adjusted for gestational age, birth weight, pulmonary hypertension, IVH > grade II, and neonatal seizure.

† Use of nitric oxide, or sildenafil, or iloprost within 1 week of birth.

However, in the nonligated group, which had higher rates of ibuprofen use to close the hs PDA, the prevalence of BPD at least moderate was significantly higher. There was no significant difference in mortality between the 2 groups (Table 1).

As seen in Table 2, the VLBWI group that underwent LL (n = 29) experienced significantly more pulmonary hypertension at ≤1 week of life. The day of surgical ligation was significantly later in the LL group (30.8 ± 28.3 vs 9.2 ± 3.4 days; $P < 0.001$) compared with the EL group. Other than those, the EL and LL groups had no significant differences for other morbidities and mortalities (Table 2).

A multivariable logistic regression analysis was performed to detect any confounding factors in relation to hs PDA surgical ligation. We included gestational age, birth weight, pulmonary hypertension, and neonatal seizures in this analysis. Pulmonary hypertension was consistently associated with hs PDA surgical ligation (Table 3).

No serious complications associated with ligation such as vocal cord paralysis,[12] hemorrhage, air leaks, or wound infection[13] were reported. The mean surgical time was an average duration of 22 minutes.

4. Discussion

The prevalence of hs PDA is inversely related to maturity. While the hs PDA affects 60% of extremely preterm infants born weighing less than 1000 g,[14] the incidence of hs PDA among VLBWIs in the present study was 35.6%, which was a similar finding to the previously reported 30% incidence of PDA among VLBWI.[1] Prolonged hs PDA results in hemodynamic and respiratory instability due to the diastolic steal phenomenon by large ductal shunting, which leads to an increased duration of mechanical ventilation, subsequent BPD, and other adverse outcomes. In addition to BPD, NEC is also a frequently reported postnatal morbidity of pulmonary overcirculation.[15–17] Prone to these morbidities, 70% of those born before 28 weeks gestation reported to receive either medical or surgical therapy to close the PDA.[18] Further, early surgical ligation was advocated as the optimal therapy for PDA due to definitive ductal closure with minimal morbidity and mortality.[9]

In our study, hs PDA infants who ligated had a higher incidence of BPD (Table 1). The nonligated group had significantly more oral ibuprofen use than did the ligated group ($P = 0.034$). The less use of oral ibuprofen use in the ligated group may indicate more unstable clinical conditions or contraindications to oral ibuprofen. Higher BPD incidence may be due to longer exposure to pulmonary edema resulting from an hs PDA which may take longer time to definitely close ductus via surgical ligation. A recent study in premature baboons demonstrated altered pulmonary mechanics and arrested alveolarization after 14 days of exposure to moderate-sized ducti.[19] Overcirculation of the lungs in humans can also result in microcirculatory lung damage.[20] Szymankiewicz et al[21] demonstrated that both clinical and radiographic evidence of pulmonary edema and lung compliance were improved after surgical ligation. In addition, the study by Lee et al[22] showed an association between multiple courses of COIs before PDA ligation and an increased incidence of BPD. The early resolution of pulmonary edema by definite surgical ligation of hs PDA may be helpful in improving lung mechanics and may lower the incidence of severe BPD.

In the ligated group, we found no differences in morbidities and mortality between the EL and LL groups (Table 2). However, pulmonary hypertension at ≤1 week of life was significantly more associated with the LL group (Table 2). Pulmonary hypertension at ≤1 week of life often occurs in reduced and restricted lungs with low compliance. The higher incidence of pulmonary hypertension in ligated patients may also indicate more severe lung conditions in this group compared to the nonligated group. In addition, persistent right-to-left shunting through the ductus may delay the surgical ligation timing. Some authors additionally report several cases of pulmonary hypertension after ibuprofen use for PDA.[23,24]

Among the 58 ligated infants, 27 (46.6%) infants first received oral ibuprofen that failed to close the hs PDA before surgical ligation (Table 1). However, the incidence of oral ibuprofen use was not significantly different between the EL and LL groups (Table 2). Additional studies also have proved that treatment failure is more common among VLBWIs and infants with severe cardiopulmonary compromise.[25] Mellander et al[26] found that pharmacologic failure in neonates with cardiopulmonary

compromise results in prolonged ventilator support after surgical ligation of PDA. Surgical ligation is an effective and definitive procedure associated with low mortality, and when indicated, timely ligation of the hs PDA may be considered to reduce the effects of extended exposure to hemodynamic instability in VLBWIs. The optimal timing for surgical ligation is still debatable. In the present study, no differences in the rates of morbidities and mortalities were found between the EL and LL groups, suggesting that the optimal surgical time for hs PDA ligation is at any point in time in which hs PDA has been diagnosed, persists, and cannot be closed by oral medication. Without timely intervention, pulmonary overcirculation may lead to considerably increased morbidity involving BPD, NEC, and renal impairment due to the "diastolic steal phenomenon." We adopted the McNamara criteria for identifying hs PDA which focuses on hemodynamic changes in clinical and echocardiogram findings and allows for easier identification of hs PDA while reducing unnecessary interventions for innocent PDA. We believe that VLBWIs would benefit from the refinement of the criteria for identifying PDA and from the close monitoring and conservative management of hs PDA until it can be determined whether surgical ligation is required. We are aware of some limitations of our study: the retrospective study design might not be the proper way to confirm examined relationships, the relatively small sample size of the study groups, and many clinical conditions comingle originating from prematurity itself.

In conclusion, EL was not significantly associated with increased hospital morbidities and mortalities in VLBWIs with hs PDA. Surgical ligation of PDA is a safe and effective treatment and should be performed in selected hs PDA infants to reduce BPD severity. The hs PDA infants who experienced more severe lung dysfunction with lower lung compliance (e.g., pulmonary hypertension at $\leq$1 week of life) may be at risk for requiring surgical ligation of hs PDA.

Acknowledgments

I would like to thank Dr Tae-Hoon Kim, a cardiologist, for his help and support in the assistance with the statistical analysis. Dr Tae-Hoon Kim gave permission to be named.

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