

Primary Surgical Closure Should Be Considered in Premature Neonates with Large Patent Ductus Arteriosus

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Background: Treatment for patent ductus arteriosus (PDA) in premature infants can consist of medical or surgical approaches. The appropriate therapeutic regimen remains contentious. This study evaluated the role of surgery in improving the survival of premature neonates weighing less than 1,500 g with PDA. **Materials and Methods:** From January 2008 to June 2011, 68 patients weighing less than 1,500 g with PDA were enrolled. The patients were divided into three groups: a group managed only by medical treatment (group I), a group requiring surgery after medical treatment (group II), and a group requiring primary surgical treatment (group III). **Results:** The rate of conversion to surgical methods due to failed medical treatment was 67.6% (25/37) in the patients with large PDA (≥ 2 mm in diameter). The number of patients who could be managed with medical treatment was nine which was only 20.5% (9/44) of the patients with large PDA. There was no surgery-related mortality. Group III displayed a statistically significantly low rate of development of bronchopulmonary dysplasia (BPD) ($p=0.008$). The mechanical ventilation time was significantly longer in group II ($p=0.002$). **Conclusion:** Medical treatment has a high failure rate in infants weighing less than 1,500 g with PDA exceeding 2.0 mm. Surgical closure following medical treatment requires a longer mechanical ventilation time and increases the incidence of BPD. Primary surgical closure of PDA exceeding 2.0 mm in the infants weighing less than 1,500 g should be considered to reduce mortality and long-term morbidity events including BPD.

Key words: 1. Patent ductus arteriosus
2. Premature
3. Neonate

INTRODUCTION

Patent ductus arteriosus (PDA) is significantly more common in premature neonates; its incidence is 80% and 45% in premature neonates with a birth weight less than 1,250 g and 1,750 g, respectively [1]. The left-to-right shunt in PDA in premature neonates can increase the incidence of chronic pulmonary disorders, intracranial hemorrhage, necrotizing enter-

ocolitis, renal failure, and metabolic acidosis, which can be direct causes of death. The appropriate treatment regimen for PDA comprises one or more cycles of medical treatment, if warranted, prior to surgical treatment [2]. Conversely, surgical treatment may be more effective and reliable, and, in over 40% of neonates examined in several studies, should be performed in very low birth weight neonates for whom medical treatment had failed [2,3]. Presently, we report the role of

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surgical closure of PDA in the mortality, morbidity and outcomes at 1-year follow-up in premature neonates weighing less than 1,500 g.

MATERIALS AND METHODS

A retrospective study of the role of surgical closure of PDA was carried out by analyzing 68 premature neonates weighing less than 1,500 g who were diagnosed with PDA from January 2008 to June 2011. The parameters evaluated were gender, gestational age, birth weight, the size of the PDA, the signs of respiratory failure, associated intracardiac defects, presence of necrotizing enterocolitis, development of bronchopulmonary dysplasia, residual PDA, body weight after one year, mechanical ventilation time, length of hospital stay, and treatment methods. Bronchopulmonary dysplasia is a chronic lung disorder that is most common among children who were born prematurely, with low birth weights and who received prolonged mechanical ventilation. In this study, bronchopulmonary dysplasia is diagnosed by chest radiographic findings. The mechanical ventilation time was estimated from the beginning of the application of mechanical ventilation to the end of mechanical ventilation. The length of hospital stay was estimated from admission to discharge. Medical records were used to evaluate these parameters.

The primary policy of our pediatrics department in managing PDA is the use of two cycles of ibuprofen (Arfen; Lisapharma, Erba, Como, Italy) or indomethacin (Indocin; Merck Sharp & Dohme, West Point, PA, USA), regardless of birth weight and PDA size. Primary surgical closure is recommended for the patients with pulmonary hemorrhage or severe respiratory failure. In cases in which the PDA does not close, surgical closure is performed. Prior to January 2011, indomethacin was used, with ibuprofen used after January 2011.

All of the operations were performed at the neonatal intensive care unit (NICU) so as not to deliver the baby, considering the hemodynamic state of the patient. To maintain the same conditions as those in the operating room, anesthesiologists and an operating room nurse participated in the operation, and the necessary operating equipment and tools were carried to the NICU from the operating room. For anesthesia,

fentanyl citrate and vecuronium bromide were used for sedation and muscle relaxation. The operation was performed by posterolateral open thoracotomy through the left 3rd or 4th intercostal space, and the view of the operating field was obtained by retracting the lung anteriorly. All of the operations were performed by two surgeons. Typically, the double ligation method was used, but double metal clipping was used from March 2010 onwards. A thoracic tube was inserted and was removed on postoperative day 1 or 2, in the absence of problems on plain radiographs.

The subjects were divided into three groups: a group managed only by medical treatment (group I), a group requiring surgery after medical treatment (group II), and a group requiring primary surgical treatment (group III). All of the data are presented as the mean±standard deviation. The chi-square test, Kruskal-Wallis test, Duncan test, and Tukey honestly significant difference test were used to evaluate factors. Survival data analysis was performed by the Kaplan-Meier method and log-rank method. The end point of survival was defined as the first birthday or death. Findings were interpreted as statistically significant when the p-value was less than 0.05.

RESULTS

The general characteristics and associated conditions of the neonates are shown in Table 1. The patients comprised 36 males (52.9%) and 32 females (47.1%). The mean gestational age was 192±20 days and the mean birth weight was 926±286 g. The mean size of the PDA on echocardiography was 2.3±1.1 mm in diameter. Group I, II, and III consisted of 32, 29, and seven neonates, respectively. Twelve group I neonates (37.5%), 25 group II neonates (82.2%), and seven group III neonates (100%) had a PDA >2.0 mm in diameter (Table 1). The numbers of neonates with respiratory distress syndrome, associated intracardiac defects, necrotizing enterocolitis, and sepsis in each group are shown in Table 1. In group I, six patients had intracardiac defects. Three of the six had atrial septal defects. One patient had a ventricular septal defect. Two of the six had both an atrial septal defect and ventricular septal defect. In group II, eight of the patients had an intracardiac defect. All of the patients had an atrial septal

defect. In group III, five of the patients had an intracardiac defect. Four of these five also had an atrial septal defect. The remaining one had a ventricular septal defect. In group III, all of the neonates displayed pulmonary hemorrhage, symptoms of respiratory failure, and a larger diameter PDA. The reason for primary surgical closure was pulmonary hemorrhage in four patients, contraindications to indomethacin in two patients, and severe respiratory distress syndrome in one patient.

Table 1. General characteristics and associated conditions according to group

	Group I (n=32)	Group II (n=29)	Group III (n=7)
Gestational age (day)	197±22	185±15	207±13
Age at operation (day)		13±12	3±2
Birth weight (g)	969±332	842±205	1,081±279
PDA diameter (mm)	1.6±0.6	2.8±1.1	3.1±0.6
≥2.0	12 (37.5)	25 (86.2)	7 (100.0)
<2.0	20 (62.5)	4 (13.8)	0 (0)
RDS	28 (87.5)	29 (100.0)	7 (100.0)
Intracardiac defect	6 (18.7)	8 (27.5)	5 (71.4)
NEC	9 (28.1)	4 (13.8)	2 (28.6)
Sepsis	9 (28.1)	4 (13.8)	2 (28.6)

Values are presented as mean±standard deviation or number (%).

PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; NEC, necrotizing enterocolitis.

The time interval from birth to surgery was 13±12 days in group II and 3±2 days in group III.

Medical treatment failure occurred mainly in neonates with a PDA exceeding 2.0 mm. The failure rate of medical treatment in all of the evaluated neonates was 60.6% (37/61) (Fig. 1). The failure rate was statistically much higher in the patients with large PDA than with small PDA (75.6% [28/37] vs. 37.5% [9/24], p=0.003). The rate of conversion to surgical treatment was also statistically higher in the patients with large PDA than with small PDA (67.6% [25/37] vs. 16.6% [4/24], p<0.001). The total success rate of medical treatment was only 20.5% (9/44) in the patients with large PDA (Fig. 2). The complications after surgery in group II and group III occurred in two neonates. They had pneumothorax, which was managed without a problem.

Multivariate analysis for survival and death revealed no statistical significance. Eight deaths occurred in group I (25% [8/32]). The causes of death were sepsis in five patients, persistent pulmonary hypertension in one patient, pulmonary hemorrhage in one patient, and disseminated intravascular coagulation in one patient. Two of six group I neonates underwent surgery due to an associated intracardiac defect. One neonate underwent a patch closure of a ventricular septal defect two years later. The other neonate underwent a direct closure of an atrial septal defect and ligation of the remaining

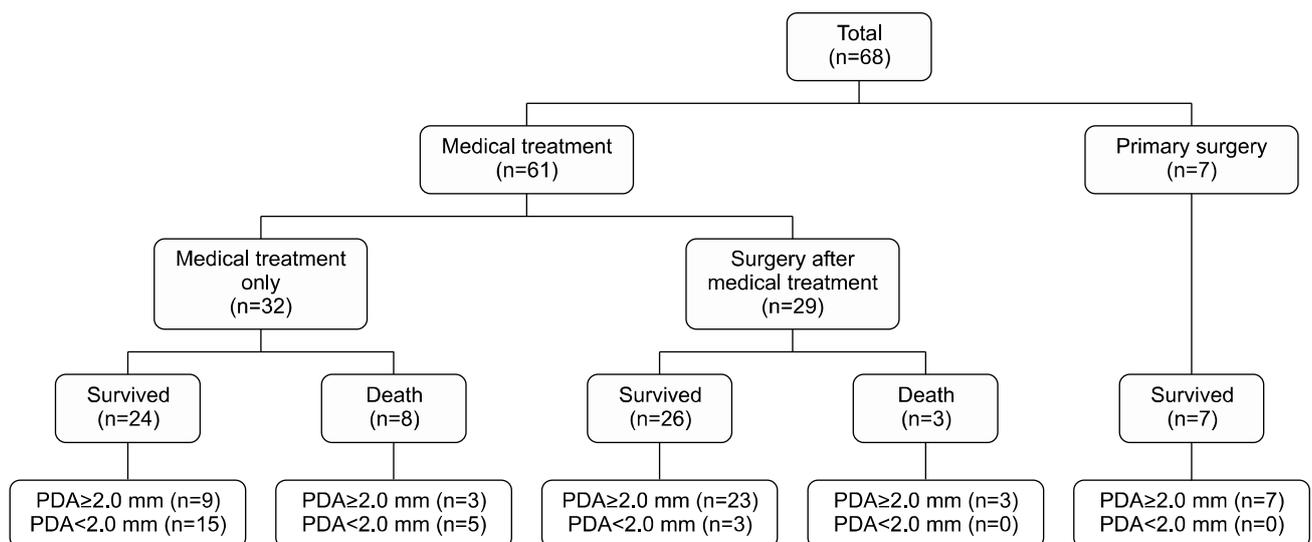


Fig. 1. Distribution of neonates by treatment method and their corresponding diameter of patent ductus arteriosus (PDA).

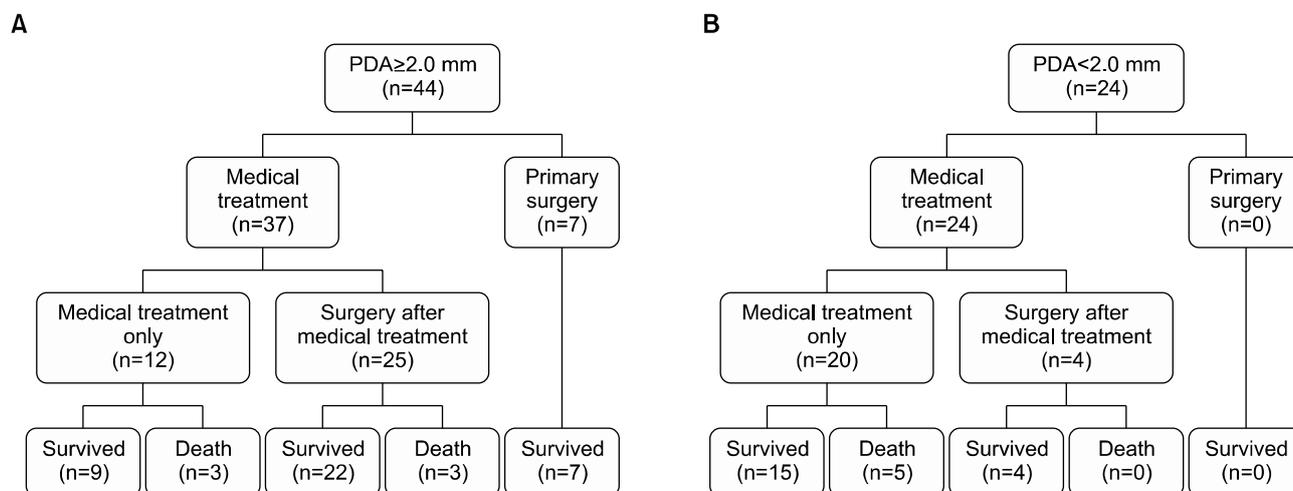


Fig. 2. (A) Distribution of neonates with patent ductus arteriosus (PDA) size over than 2.0 mm by treatment method. (B) Distribution of neonates with PDA size less than 2.0 mm by treatment method.

Table 2. Result of treatment according to group

	Group I (n=32)	Group II (n=29)	Group III (n=7)	p-value
Residual patent ductus arteriosus	11 (34.3)	0 (0)	0 (0)	0.001
Death	8 (25)	3 (10.3)	0 (0)	0.141
Bronchopulmonary dysplasia	22 (68.7)	25 (86.2)	2 (28.5)	0.008
Mechanical ventilation time (day)	15±23	35±26	15±12	0.002
Hospital stay (day)	56±32	89±36	72±21	0.151
Body weight after one year (g)	5,903±3,868	7,072±2,709	8,314±1,433	0.063
Amount of weight gain (g)	5,110±3,369	6,323±2,416	7,256±1,412	0.059

Values are presented as number (%) or mean±standard deviation. The chi-square test, Kruskal-Wallis test, Duncan test, and Tukey honestly significant difference test are used to evaluate factors.

PDA one year later. Three survivors in group I had residual PDA. Two of the three had no symptoms of PDA and are under clinical observation. The remaining neonate was once treated with indomethacin and then the PDA (size=1.7 mm) was closed. However, at the 6 month follow-up, the PDA was found to have enlarged from 1.7 to 3.4 mm, which necessitated surgery. No residual PDA was detected in group II or group III neonates. Three of the group II neonates died. Two patients died of irreversible hemodynamic instability that was caused by preoperative pulmonary hemorrhage, pulmonary edema, necrotizing enterocolitis, and sepsis. Another one died of severe respiratory distress syndrome that had not been corrected by surgery. The birth weights of the three neonates that died were 735, 895, and 995 g. There was no surgery-related mortality. No deaths occurred in group III.

Data concerning the development of bronchopulmonary dysplasia (BPD), mechanical ventilation time, length of hospital stay, body weight after one year, and amount of weight gain are shown in Table 2. Group III displayed a statistically significantly low rate of developing BPD (p=0.008; 68.7% in group I, 86.2% in group II, and 28.5% in group III). Other risk factors of BPD such as gender, birth weight, gestational age, mechanical ventilation time, and necrotizing enterocolitis revealed no statistical significance. The mechanical ventilation time was significantly longer in group II (p=0.002; 15±23 days in group I, 35±26 days in group II, and 15±12 days in group III). The length of hospital days showed no statistical significance (p=0.151). Group III showed the largest body weight and amount of weight gain, but no specific relationship reached statistical significance (p=0.063).

DISCUSSION

Before birth, the blood in neonates flows from the right ventricle into the descending aorta through the ductus arteriosus. After birth, a newborn takes its first breath after clamping of the umbilical cord and pulmonary circulation begins, after which pulmonary vascular resistance decreases and blood flow to the lungs increases. These events lead to an increase in the oxygen concentration in the arterial blood and constriction of the smooth muscle of the ductus arteriosus, and results in reduction of the internal diameter and length of the ductus arteriosus [4]. Later, the endothelial cells proliferate in the vessel, the subendothelial layer is damaged, and the ductus arteriosus is closed with connective tissue formation [5,6]. Usually, the ductus arteriosus is completely sealed after 2 to 3 weeks. PDA is defined as an abnormal persistence of an open lumen in the ductus arteriosus.

Definite left-to-right shunt in premature neonates with PDA can cause many problems. After birth, as the pulmonary vascular resistance decreases, blood flow to the pulmonary vessels increases and results in reduction of lung compliance. Consequently, the mechanical ventilation support time is lengthened, which ultimately induces structural changes such as BPD [5,7,8]. In addition, the shunt can cause congestive heart failure and reduce cardiac output, resulting in decreased blood flow to the lower extremities. Diastolic steal to the pulmonary artery reduces blood flow to the abdominal organs and may lead to necrotizing enterocolitis [9]. The incidence of PDA has been estimated to be 10% to 60% according to gestational age, and varies [10]. To evaluate the incidence of significant PDA, several diagnostic indicators, such as cardiac murmur, tachycardia, bounding pulse, widened pulse pressure, and dyspnea (increase of oxygen demand and frequent adjustment of the ventilator), can be used [11]. In addition, echocardiography and Doppler sonography can be used to diagnose significant PDA using the following four criteria: 1) demonstration of a left-to-right shunt, 2) a left atrial:aortic root ratio exceeding 1.3, 3) ductal size >1.5 mm, and 4) disturbed diastolic flow in the main pulmonary artery with a diastolic backflow in the aorta immediately below the ductus arteriosus [12]. For the medical treatment of PDA, oxygen supply, fluid restriction, diuretics, and medications can be

used. Surgical treatment involves ligation of the PDA. However, until now, the indications for medical versus surgical treatment of PDA have been contentious. Primary surgical ligation of PDA might be safer and more effective because of a high failure rate and the complications of medication in premature neonates [5,6]. It has been opined that medical treatment should be performed prior to surgical methods, since the operation could cause unstable blood pressure, respiratory disorders, infection, intracranial hemorrhage, chylothorax, and paralysis of the laryngeal nerve [13]. In our cases, we had not experienced any of these complications.

It can be difficult to determine whether medical or surgical treatment should be performed first [14]. Currently, surgery is performed in cases in which medical treatment has failed or is not feasible due to accompanying problems, although the timing of the operation remains controversial [15]. It has been recommended that an operation should be performed if the ductus arteriosus remains patent even after administering two cycles of ibuprofen, as the morbidity caused by the PDA might increase with time in premature neonates [16]. In one study, two cycles of ibuprofen were appropriate since some of the cases showed PDA closure after this regimen, even in cases in which the PDA was not closed after one cycle of ibuprofen [17]. Jhaveri et al. [18] reported that 72% of patients who received medical treatment underwent surgery, and that gestational age was influential according to the analysis of the operative group. In that study, 81% of premature neonates with a gestational age of 24 to 25 weeks underwent an operation, 56% of premature neonates with a gestational age of 26 to 27 weeks underwent an operation, and 14% of premature neonates with a gestational age of 28 to 29 weeks underwent an operation, indicating the importance of gestational age concerning surgery. Presently, the primary surgical ligation group showed less development of BPD and shorter mechanical ventilation time in neonates with a PDA diameter exceeding 2.0 mm. Furthermore, if medical treatment fails, the incidence of BPD is higher and the length of hospital stay is longer, which diminishes the quality of life. Considering that the rate of conversion to operative methods is about 67% because of the absence of response to medical treatment in patients with PDAs exceeding 2.0 mm in diameter, early surgical treatment for PDA can be a treatment

method worth considering for premature neonates weighing less than 1,500 g. Ligation of PDA or metal clipping through a left thoracotomy is the most commonly used approach for the operation. Suture material is usually used for ligation of PDA. However, considering the histologic features of PDA in premature neonates, the use of metal clips has recently been recommended after a minimally invasive approach to reduce the operation time and complications such as bleeding [19]. In this study, a double ligation with suture material was performed until April 2010, and metal clips were used from March 2010 onwards. More recently, minimally invasive techniques have been introduced, and successful results have been reported with thoracoscopy in extremely low birth weight neonates weighing less than 1,000 g. However, it provides a poor view of the surgical field, and there is a need for conversion to open thoracotomy in cases in which it is difficult to control bleeding. Moreover, thoracoscopy needs to be performed in the operating room because of the equipment required, which means that the patients also need to be taken to the operating room [20]. A study performed in Korea reported good results for the operation through a small posterior thoracotomy, which could reduce the incidence of injury to the lung and pleura, and for which there was no need to insert a thoracic tube [21]. In the study, 24 premature neonates were enrolled. Eight premature neonates died because of poor preoperative conditions. There was no surgery-related mortality.

Raval et al. [22] reported that the patients who received surgical treatment after failure of medical treatment had a lower survival rate than did the patients who received only medical treatment due to patient characteristics, although this difference was not statistically significant. However, in our study, the total success rate of medical treatment was only 20% in the patients with large PDA. However, survival after surgical treatment was high even if the patients with medical treatment failure were included. Moreover, there was no operative mortality and a low incidence of BPD in the patients who underwent primary surgical closure because of poor medical condition (group III). From these data, we believe that overall mortality and morbidity could have been reduced if all of the premature patients weighing less than 1,500 g with large PDA (≥ 2 mm) had received primary surgical clo-

sure instead of medical treatment. Our data clearly showed that surgical closure after failed medical treatment prolonged mechanical ventilation time and increased incidence of BPD. Considering long-term quality of life for premature infants, postnatal adverse events and mechanical ventilation time after birth must be minimized. We strongly believe that primary surgical closure of large PDA can reduce mortality and morbidity for the premature patient weighing less than 1,500 g. However, a randomized prospective study should be required to prove whether primary surgical closure is superior to initial medical treatment in the premature baby with large PDA (≥ 2 mm).

CONCLUSION

Medical treatment has a high failure rate in infants weighing less than 1,500 g with PDA exceeding 2.0 mm. Surgical closure following medical treatment requires a longer mechanical ventilation time and increases the incidence of BPD. Primary surgical closure of PDA exceeding 2.0 mm in infants weighing less than 1,500 g should be considered to reduce mortality and long-term morbidity events including BPD. This study has limitations due to the total number of premature neonates, its retrospective design, and the short follow-up period.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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