CASE REPORT

Prematurity with Unilateral Diaphragmatic and Vocal Cord Paralysis Following Patent Ductus Arteriosus Ligation

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Abstract
Patent ductus arteriosus (PDA) remains an important cardiovascular problem in term and pre-term infants. Consequent hemodynamically significant left-to-right shunt may impact all organ systems. There are several kinds of interventions to minimize adverse effects, including cycloxygenase (COX) inhibitors, paracetamol, and surgical ligation. Surgical ligation is usually performed when medical therapy with COX inhibitors fails or is contraindicated. However, some complications like intra-operative bleeding, pneumothorax, left recurrent laryngeal nerve paralysis, respiratory compromise, infection, chylothorax, intracranial hemorrhage, and left phrenic nerve injury, may happen. This report is on a pre-term infant with clinically significant PDA. After PDA ligation, he suffered from paralysis of the left diaphragm and left vocal cord, with associated respiratory distress, ventilator support dependence, prolonged hospitalization, poor body weight gain, and feeding difficulty. Routine survey of diaphragmatic dysfunction and vocal cord paralysis should be arranged for infants who undergo surgical ligation. (J Pediatr Resp Dis 2015;11:52-58)

Key words: Patent ductus arteriosus, surgical ligation, diaphragmatic paralysis, vocal cord paralysis, seizure

INTRODUCTION

The ductus arteriosus is a vascular connection between the aorta and main pulmonary trunk during the fetal period. It diverts blood flow from the pulmonary trunk (or proximal left pulmonary artery) to the descending aorta. With the foramen ovale, it plays an important role in bypassing pulmonary flow. After birth, functional closure rapidly occurs, within 24-96 hours. It then undergoes obliteration and eventually forms the ligamentum arteriosum. If spontaneous and permanent closure fails, a patent ductus arteriosus (PDA) is established.

The incidence of PDA ranges from 0.03% to 0.08% among term infants.¹ with about 30% in very low birth weight infants (VLBW, <1500 grams) and 65% in extremely low birth weight infants (ELBW, <1000 gm).²³ The adverse hemodynamic effects of a significant left-to-right shunt through the PDA impact on all organ systems, particularly the brain, lungs,
kidneys, and intestines, and increase the risk of intraventricular hemorrhage (IVH), broncho-pulmonary dysplasia (BPD), renal failure, and necrotizing enterocolitis (NEC).4

Therapeutic interventions to minimize the adverse effects or to close the PDA include supportive care (e.g. intensive monitoring, fluid restriction, increasing hematocrit, and ventilator support), cyclooxygenase (COX) inhibitors (e.g. indomethacin and ibuprofen), paracetamol.5 and surgical ligation.

Surgical ligation is usually performed when the medical therapy of COX inhibitors is failed or contraindicated. It is performed directly through an open method of left postero-lateral thoracotomy or indirectly through a minimal invasive technique of video-assisted thoracoscopic surgery (VATS).6,7 The success rate of surgical closure is high and the surgery-related mortality is low.8 However, ligation is sometimes associated with complications, such as intra-operative bleeding, pneumothorax, left recurrent laryngeal nerve paralysis, respiratory compromise, infection, chylothorax, intracranial hemorrhage (ICH), and left phrenic nerve injury.8,9

Here is a report on a pre-term infant suffering from clinically significant PDA. He underwent surgical ligation after two courses of oral ibuprofen therapy. Post-operatively, he developed a combination of left vocal cord paralysis (LVCP) and left diaphragmatic paralysis.

**CASE REPORT**

A male pre-term neonate (twin B) with gestational age of 32 weeks and 2 days and birth body weight of 1640 gm was born via cesarean section delivery to a healthy 32-year-old mother (G1P1A0). The Apgar scores were 8 at 1 minute and 9 at 5 minutes after birth. The birth body weight of twin A, his brother, was 1730 gm. There was no particular peri-natal insult.

The twins were both transferred to the neonatal intensive care unit (NICU) for progressive respiratory distress with tachypnea, nasal flaring, subcostal retraction, and expiratory grunting and treated with nasal continuous positive airway pressure (NCPAP). Initial chest radiography revealed respiratory distress syndrome, grade II.

Echocardiography on the 7th day of life to evaluate the heart murmur revealed a medium sized PDA (1.1 mm in diameter) with continuous left-to-right shunt. The left atrial/aortic root ratio (LA/Ao) was 1.6:1. Medical treatment with oral ibuprofen (3-day course) on the 11th to 13th day of life closed the PDA. However, after two days, the PDA re-opened (1.6 mm in diameter) with significant left-to-right shunt. A second course of oral ibuprofen was given on the 21st to 23rd day of life but did not help.

Due to progression of the PDA (2.3 mm in diameter) with left ventricular enlargement, surgical closure was arranged. The PDA ligation was performed on the 29th day of life with left postero-lateral thoracotomy via the fourth intercostal space intra-pleurally using both silk and clips firmly.

Nevertheless, frequent episodes of desaturation were observed a few hours after the operation. Increased vascular markings and mixed pattern opacities over both lungs, obvious left-sided hypo-inflation, and eventration of left diaphragm were demonstrated by chest radiography, compared to the pre-operative study (Fig. 1). The patient also had seizures and brain sonography revealed intracranial hemorrhage over the right para-frontal horn area.

Extubation was successfully performed 4 days post-operatively and respiratory support was shifted to NCPAP. However, symptoms of hoarseness and weak cry developed 2 weeks after the surgery. Intravenous injection of dexamethasone and inhalation of epinephrine were given but to no avail. Considering post-ligation LVCP, flexible bronchoscopy was arranged, revealing compatible results (Fig. 2). Thoracic ultrasound also showed paradoxical movement of the left diaphragm with respiration, elevating in the inspiratory phase and depressing in the expiratory phase.

Under the diagnosis of LVCP and left diaphragm paralysis post-PDA ligation, treatment strategies like adequate respiratory support, protection of airway, enough energy intake, thickened formula, multivitamin supplementation, and rehabilitation program were
initiated. Frequent desaturation and apnea occurred initially but gradually subsided. Feeding intolerance and periodic pneumonia were still noted.

On serial chest radiography, the left diaphragmatic paralysis finally improved 2 months after the operation (Fig. 3). The duration of NCPAP dependence after extubation was 54 days and the total length of hospitalization was 126 days. However, hoarseness and weak cry did not improve satisfactorily before his discharge. Persistent LVCP with right-sided compensation was observed on out-patient follow-up 4 months after the surgery.

On the other hand, his twin sibling also suffered from hemodynamically significant PDA and received oral ibuprofen on the 7th to 9th day of life as initial treatment. On the 12th day of life, surgical closure by the same surgeon using the same procedure was done due to the poor response to COX inhibitors. There was no obvious post-operative complication. The duration of NCPAP dependence after extubation was 3 days. The total length of hospitalization was 39 days.

This pair of twins underwent regular medical check-up and prophylactic vaccination at the out-patient department (OPD). Twin B was hospitalized for five more times before the corrected age of 18 months, including four times due to acute bronchiolitis. In contrast, twin A was just admitted just once before the corrected age of 18 months, for a chief complaint of acute bronchiolitis.

Figure 1.
(A) Pre-operative chest radiography was taken to confirm the location of the tip of the endotracheal tube.
(B) Post-operative study revealed increased vascular markings and mixed pattern opacities over both lungs, obvious left-sided hypo-inflation, and eventration of the left diaphragm.

Figure 2
On flexible bronchoscopy, (A) both vocal cords abducted normally in the inspiratory phase and (B) the right vocal cord moved smoothly in the expiratory phase, but left vocal cord was fixed laterally.
DISCUSSION

Pharmacologic therapy of intravenous indomethacin and ibuprofen lysine, non-selective cyclooxygenase (COX) inhibitors, is used as the initial treatment for PDA closure through prostaglandin synthesis inhibition, since prostaglandin E2 (PGE2) promotes the patency of the ductus arteriosus. Due to the expensive cost of intravenous preparation, oral ibuprofen is prescribed in developing countries. In the study hospital, oral ibuprofen is the choice of pharmacologic agent. With this pharmacotherapy, the success rate of PDA closure is from 75% to 93%, with a relapse rate up to 33%.10-12

Percutaneous PDA occlusion is an alternative for patients beyond infancy.13 The procedure is less invasive than surgical ligation and shortens the period of hospitalization. However, it is not cost-effective and is usually associated with complications in small infants.14 Surgical ligation is applied when the COX inhibitors fail or are contraindicated. Complications include ductal tear, hypertension, intra-operative bleeding, pneumothorax, LVCP, respiratory distress, infection, chylothorax, ICH, NEC, and left diaphragm paralysis.7-9 The reported rates of intra- and post-operative complications are about 26% and 57%, respectively.15

Injury to the left recurrent laryngeal nerve leads to LVCP. The reported incidence following surgical ligation is highly variable (range, 0.7-67%).8,16 A higher prevalence is observed in infants with smaller gestational age, lower birth weight, and lower body weight at the time of surgery.17

A comparison of pre- and post-operative nasopharyngolaryngoscopy or flexible bronchoscopy provides a relatively direct evidence for LVCP following ligation. However, it is not routinely performed because of the infants’ unstable condition and the expensive costs. Infants with LVCP often present symptoms such as inability to wean from respiratory support, post-extubation stridor, weak cry, hoarseness, feeding difficulty, easy choking, and recurrent aspiration pneumonia. The impression of LVCP is usually considered when the above symptoms develop. Thus, the prevalence of LVCP
following PDA ligation may still be underestimated.

The recurrent laryngeal nerve, a branch of the vagus nerve, provides innervation to voicing, breathing, and swallowing. Any impairment of airway protection will cause micro-aspiration, which may lead to recurrent respiratory tract infection and long-term reactive airway disease. Infants with LVCP are also prone to regurgitate and suffer from feeding intolerance. Thus, LVCP may be associated with poorer body weight gain, longer hospital stay, and long-term neuro-developmental impairment.

Compared to his twin sibling, the patient had relatively poorer performance in body weight gain at the time of discharge (corrected age of 9 weeks and 4 days) and at the corrected age of 12 and 18 months of 4.3, 9.0, and 10.5 kilograms, respectively. The body weight of twin A at the same time points was 5.7, 10.0, and 11.8 kg, respectively. Similar results were noted on the duration of NCPAP dependence after extubation, total length of hospitalization, and number of hospitalizations for acute bronchiolitis.

The left recurrent laryngeal nerve branches from the vagus nerve at the aortic arch near the heart. It is prone to injury (e.g. traction, contusion, resection, or ligation) for its proximity to the PDA ligation site. Complete recovery of the LVCP may be achieved in a few months. However, more permanent paralysis may develop if the LVCP lasts for more than 6 months. It seldom causes long-term problems in feeding or airway protection because the right vocal cord usually compensates adequately over time.

Diaphragm paralysis resulting from phrenic nerve injury is well known as a surgical complication of congenital heart disease. The incidence in children after cardiac surgery ranges from 5.4% to 20%. However, most of these cases have undergone complicated cardiac surgery. Left diaphragm paralysis following PDA ligation is relatively rare, especially in pre-term infants. As the left recurrent laryngeal nerve, the anatomic course of the left phrenic nerve makes it vulnerable during PDA ligation. In the thoracic course, it descends along the left subclavian artery, passes laterally to the aortic arch, and continues descending along the left lateral surface of the pericardium before reaching the diaphragm. Diaphragm paralysis in infants, especially in ELBW prematurity, usually causes respiratory distress, prolonged need for ventilation, recurrent pneumonia, poor body weight gain, and even death. Management includes adequate nutrition (e.g. multivitamins), ventilation support, and maybe surgical intervention of diaphragmatic plication.

Prolonged ventilator support with or without intubation is associated with nosocomial infections and BPD. Thus, diaphragmatic plication should be considered for unsuccessful weaning of ventilation. Electro-physiologic examination of phrenic nerve latencies and diaphragmatic action potential (DAP) amplitudes is used in children after cardiac surgery. Persistently abnormal DAPs for more than 2 weeks is an indication of diaphragmatic plication because the paralysis is usually temporal and reversible within 2-8 weeks. Diaphragmatic plication is safe and easy, even in ELBW infants, but the timing remains controversial.

To date, there has been no previous case report regarding the combination of LVCP, left diaphragm paralysis, and ICH following PDA ligation in infants. Ligation is sometimes associated with complications because the dissection around the ductus arteriosus increases the risk of vascular and nerve injury. In this case, the procedure was done with both silk and clip. More dissection around the ductus and longer operation time were needed, which could have increased the risk of post-operative complications. Such complications may lead to differences among siblings of multiple births.

CONCLUSIONS

Surgical ligation offers satisfying success for the management of clinically significant PDA, but the associated complications may be underestimated and are sometimes serious. Physicians should provide complete information regarding complications for the patient’s family before surgery. Routine survey of the vocal cord and diaphragm paralysis for all patients receiving PDA ligation is suggested.

REFERENCES
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