Current treatment options for the management of patent ductus arteriosus

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Abstract: Pharmacological and/or surgical closure of a hemodynamically significant patent ductus arteriosus (PDA) in the very premature infant has been the standard of care over the past few decades. However, the rationale for closure of PDA has recently been challenged. In this article, three ways of approaching the closure of PDA including pharmacological treatment, catheter intervention, and surgical intervention, are reviewed in detail. In addition, the different treatment strategies applied in clinical care are evaluated with a focus on the discussion of the available evidence of PDA treatment in the literature.

Keywords: patent ductus arteriosus, premature infant, treatment option

Over the last three decades, knowledge about fundamental and clinical aspects of the ductus arteriosus has substantially improved, leading to considerable progress in the management of various cardiac diseases including patent ductus arteriosus (PDA). PDA is a frequently occurring pathological congenital cardiac condition in low birth weight premature neonates. The consequences of a significant left-to-right shunting through the PDA may present hemodynamic and respiratory importance.[1] Spontaneous closure of the PDA in normal birth weight neonates occurs in 3 days, but it may persist longer in the premature baby.[2] The identification of the mechanisms regulating ductal patency led to the design of pharmacological drugs to achieve medical closure of PDA in the premature infant, or inversely to maintain patency of PDA in neonates with ductus dependent congenital heart diseases. Concurrently, widespread availability of echocardiography has improved the detection of congenital PDA, resulting in earlier treatment. Closure of PDA, either by surgery or transcatheter techniques, can now be achieved safely in relatively large patients, resulting in a decrease in the incidence of severe complications of PDA. In this article, both updated and alternative treatments will be discussed. PDA often complicates the clinical course of neonates born prematurely and increases their short- and long-term morbidity. PDA is present in up to 70% of preterm infants born before 28 weeks gestation.[1] Treatment of PDA remains an ongoing debate among neonatologists for various reasons, including the timing, the criteria, and the methods for its closure. We will discuss these in the following sections. We will also show our recent surgical results for PDA clipping of very low birth weight babies in our institution.

Pharmacological treatment of PDA in preterm infants

Muscular constriction produces a region of ischemic hypoxia in the middle of the ductus muscle media that initiates the process of permanent closure of PDA. This is a

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theoretical background to attempt pharmacological closure of PDA by inducing muscle constriction of PDA. A non steroidal anti-inflammatory drug such as indomethacin[3] has been traditionally used as the treatment of choice for PDA. Its use, however, has waned due to the recognition of renal, cerebral, and gastrointestinal complications associated with the administration of this drug. Other non steroidal anti-inflammatory drugs have been investigated, but either the profile of adverse effects was unfavorable, as in the case of mefenamic acid, or their efficacy was less than that of indomethacin for PDA closure. More recently, ibuprofen has emerged in clinical practice as it has been reported to have lower nephrotoxicity[4-6] if used enterally. However, since renal perfusion, Glomerular Filtration Rate (GFR), and dieresis in early neonatal life strongly depend on the vasodilator effects of prostaglandins on the afferent glomerular arterioles, ibuprofen, like other cyclooxygenase (COX) inhibitors may not be exempt from causing some undesirable renal effects. A previous paper[7] reviewed ten trials for meta-analysis of indomethacin versus ibuprofen for PDA in the preterm infant. The trials compared intravenous indomethacin versus intravenous ibuprofen: nine trials compared intravenous indomethacin versus placebo and one trial compared intravenous ibuprofen versus placebo. The results suggested that both intravenous indomethacin (pooled relative risk [RR] 2.39, 95% CI 2.05–2.78) and intravenous ibuprofen (RR 2.40, 95% CI 2.03–2.84) closed a PDA more effectively than the placebo. Intravenous ibuprofen was associated with an approximately 30% greater risk of chronic lung disease than intravenous indomethacin (RR 1.28, 95% CI 1.03–1.6). Other papers[8,9] suggested no significantly greater benefits from ibuprofen administration. When administered for prophylaxis, ibuprofen has no effect on the prevention of intraventricular hemorrhage (IVH) unlike indomethacin.[3] A trial of continuous infusion versus intermittent bolus doses of indomethacin for PDA closure[10] suggested no statistical difference between the bolus and continuous groups for the secondary outcomes of reopening of PDA, neonatal mortality, IVH, and necrotizing enterocolitis.

Transcatheter PDA occlusion

Relatively large patients with PDA can be treated by catheter intervention, which has become a more common treatment in such patients than surgical intervention. Occlusion of PDA was first described in 1971 with an Ivalon plug.[11] This was followed by Rashkinds et al who used a hooked single disk device in 1979 and a double disk device in 1987.[12] Cambier et al[13] reported a small series using Gianturco

coils to occlude small PDAs. The major advantage of this technique was the use of a small (5 Fr.) delivery system. Since then, transcatheter occlusion of PDAs with a variety of devices and innovative techniques has been reported.[14-22] Both safety and efficacy have been established in many series, and this treatment modality has become a standard of care at many centers except in very low birth weight patients or those with unsuitable anatomy, such as the type B (also known as the AP window type) PDA.[23] The most common devices currently used are various kinds of coils and the AMPLAZER™ ductal occluder device. Many prograde and antegrade techniques have been developed to deliver coils to maximize occlusion and to minimize the risk of coil embolization.[24-26]

Indications for PDA occlusion are elimination of pulmonary overcirculation and subsequent development of obstructive pulmonary vascular disease, as well as prevention of endocarditis and/or endarteritis. There is controversy related to occlusion of the so-called silent ductus. There is little data on the benefits of occluding the silent ductus because of its small size, and presumably, the lack of significant flow turbulence and endothelial damage. In those patients with a large PDA and bidirectional flow due to pulmonary vascular disease, occlusion may be indicated only if the pulmonary lung bed shows some reactivity to pulmonary vasodilator therapies.[27,28]

Surgical clipping/ligation of PDA

The consequences of a significant left-to-right shunt through the PDA may present hemodynamic and respiratory instability.[29] Whilst awaiting spontaneous closure of PDA or pharmacological intervention, prolonged endotracheal intubation, mechanical respiratory support, and related problems may complicate the condition. Surgical closure is an option for cases where a medical intervention may not be sufficient. PDA ligation produces permanent ductus closure, improves pulmonary mechanics, and decreases the need for prolonged ventilator support. Recent studies, however, suggest that in addition to the known surgical complications that may accompany the procedure such as pneumothorax, recurrent nerve palsy,[30] and IVH,[31] the ligation itself may directly contribute to some of the neonatal morbidities. Previous studies have shown that early surgical ligation decreases alveolar water clearance, impedes lung growth, and increases the expression of genes involved with pulmonary inflammation.[32] Several studies have demonstrated that infants treated with surgical ligation

of PDA had a significant increase in adverse outcomes.[33–35] The timing of surgery is still a controversial issue. One recent report suggested that the prolonged patency of the PDA in preterm infants is related to increased morbidity, including bronchopulmonary dysplasia and acute renal failure.[36] They suggested that surgical ligation of PDA is a safe and effective treatment and should be done soon after two complete cycles of ibuprofen, especially in patients at a younger gestational age (<25 weeks), lower body weight at birth, and a higher incidence of symptomatic hypotension, in order to improve the clinical outcome.[36] Another retrospective study looking at the timing of the surgical intervention suggests that early ligation (<14 days of life) of medically refractory PDA in very low birth weight premature infants improves enteral feeding tolerance and reduces total parenteral nutrition and ventilator use.[30] A recent observational study indicated an increased risk for one or more of the following outcomes associated with PDA ligation: chronic lung disease, retinopathy of prematurity, and neurosensory impairment.[37] Another paper suggested that ductal ligation poses a risk for a further decrease in already compromised cerebral oxygenation in preterm infants.[38] However the ductal clipping has been reported to have no negative effect on cerebral oxygenation.[39] It is possible that the duration of the "waiting time" and transport to another facility with surgical capacity in order to have the PDA ligated or clipped could adversely affect outcomes, as could the perioperative care. Jhaveri et al[40] compared two different treatment approaches for infants (≤27 weeks gestation) with PDAs that failed to close after indomethacin treatment: (1) the "early ligation" approach that limited the exposure to the PDA shunt by ligating the PDA soon after indomethacin failure; and (2) a "selective ligation" approach that "tolerated" the presence of the PDA shunt and used surgical ligation only if specific criteria were met. They found that the "selective ligation" approach produced a significant decrease in the rate of ductus ligation and a significant decrease in the rates of necrotizing enterocolitis and of neurodevelopmental abnormality at 18–36 months.[40,41] The delay in ligation appears to be beneficial because accumulating evidence suggests that several of the morbidities associated with ligation including post ligation hypotension,[42] vocal cord paralysis,[43] bronchopulmonary dysplasia,[44] and abnormal neurodevelopmental outcomes[41] are significantly reduced when ligation is delayed. Further investigation is warranted to determine which infants are most likely to benefit

from surgical closure and which infants might be left untreated when pharmacological approaches are no longer available.

Outcome of surgical clipping of PDA in preterm infants in our institution
Methods and materials
Our hospital is a tertiary medical care center and perinatal care center for high risk pregnancies. Premature patients with isolated PDA and very lower body weight (body weight < 1500 grams) who underwent ductal clipping between January 2006 and December 2011 are included in this study. We have used a clipping technique rather than a ligation technique as the surgical incision is only 2 cm in length. Patients with genetic disorders, and/or CHARGE syndrome, or other cardiac diseases were excluded from this study. Of the 102 patients involved in this study, 86 patients were extremely low birth weight babies (birth weight < 1000 grams). These patients were subdivided into two groups: (1) early clipping (EC) of medically refractory PDA (≤14 days), and (2) late (>14 days) clipping (LC) of medically refractory PDA after failure of medical treatment or having contraindications to medical treatment. There were 33 patients in the EC group and 69 patients in the LC group. Basic clinical features, major morbidity of prematurity, and mortality were compared.

Results
Clinical features and major outcomes between the EC and LC groups were similar (Table 1). When compared with the LC group, the EC group had earlier onset of symptomatic PDA (mean ± SD; 7.8 ± 3.0 days versus 28.5 ± 8.7 days, $P < 0.05$)

Table 1 Patient background

	Early clipping group (n = 33)	Late clipping group (n = 69)	P value
Birth in our hospital (I)	10	21	
Birth at outside hospital (O)	23	48	
I/O ratio	0.43	0.44	NS
Gestational age (weeks)	26.5 ± 3.4	25.0 ± 2.2	NS
Birth weight (grams)	693 ± 232	799 ± 324	NS
Day of life at surgery	7.2 ± 2.7	36.5 ± 46.0	
Body weight at surgery (grams)	685 ± 256	862 ± 351	$P < 0.01$

Note: All values are expressed as mean ± SD.
Abbreviations: I, births in our hospital; O, births at other hospitals; NS, not significant.

Table 2 Complications related to transportation

	EC (n = 23)	LC (n = 48)	*P* value
IVH	3	0	NS
Hypotension	I	5	NS
Hypoxia	I	6	NS
Hypothermia	I	4	NS
Unscheduled extubation	0	I	NS

Abbreviations: EC, early clipping group; LC, late clipping group; IVH, intraventricular hemorrhage; NS, not significant.

and lower body weight at surgery (685 ± 256 grams versus 862 ± 351 grams, $P < 0.01$). Among the 71 patients transported to our facility, including 23 patients in the EC group and 48 patients in the LC group, there were several adverse effects (Table 2). These include three IVH in the EC group but none in the LC group, hypotension in six patients, hypoxia in seven patients, hypothermia in five patients, and accidental extubation in one patient. One death occurred during the surgery because of aortic dissection. Of the 102 patients, 70 patients were discharged from our hospital to their referring hospitals. Of the 32 patients who remained in our hospital, their postoperative complications include recurrent nerve palsy in four patients and ductal aneurysm in one patient. Four and three deaths occurred in the EC group and the LC group, respectively, during the postoperative course. All four patients in the EC group and two patients in the LC group died due to sepsis, and one patient in the LC group died due to duodenal perforation followed by peritonitis/sepsis (Table 3). Most complications occurred in patients born in our hospital. This may be related to the fact that our institution is one of three perinatal care centers for high risk pregnancy in metropolitan Tokyo. In fact, the average body weight at surgery was significantly less in babies born in our hospital than in those born at other hospitals (685 ± 180 grams versus 828 ± 226 grams, $P < 0.05$). Although surgical ductal clipping can be done safely, transportation may be a risk for symptomatic premature infants, particularly in patients requiring early ductus clipping. Precaution for sepsis may also be warranted.

Table 3 Postoperative complications and outcome

	EC (n = I0)	LC (n = 21)	*P* value
Left recurrent nerve palsy	I	3 (3)	NS
Aneurysmal formation of PA	0	I (I)	NS
IVH	0	0	NS
Death	4 (3)	3 (3)	NS

Abbreviations: EC, early clipping group; LC, late clipping group; NS, not significant; PA, pulmonary artery; IVH, intraventricular hemorrhage; ( ), number of patients born in our hospital.

Overall, treatment of PDA in the lower body weight baby remains an ongoing debate among neonatologists for various issues such as the timing of pharmacological and surgical closure, the criteria for the treatment option, and the medication protocol for PDA closure. Based on our clinical results, we may need to change the strategy for surgical treatment of PDA in premature babies to avoid transporting sick patients to our facility. Further investigation is also warranted to determine which infants are most likely to benefit from surgical closure of PDA and which infants are best left untreated when pharmacological approaches are no longer available.

Disclosure

The authors report no conflict of interest in this work.

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