Treatment Options of Patent Ductus Arteriosus

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Abstract

Background: Small PDA that does not cause symptoms should be followed medically for 6 months without surgical ligation because of the possibility of spontaneous closure. If left untreated, the mortality rate for PDA is 20% by age 20 years.Although there is no clear evidence of clinical efficacy, various approaches including fluid restriction, increasing PEEP, permissive hypercapnia, maintaining a high haematocrit and higher target SpO2 (89-94%) have all been used as part of a 'conservative' approach to managing a hsPDA.There is some evidence that furosemide stimulates renal synthesis of prostaglandin E2 (a dilator of the ductus arteriosus) and delays ductal closure. The risk of PDA is greater with furosemide compared with chlorothiazide. Furosemide is associated with nephroand ototoxicity.Ibuprofen is effective in achieving ductal closure in around 70-80% of cases . There is some evidence that oral therapy and higher dosage regimens are associated with higher closure rates.Paracetamol has comparable efficacy to ibuprofen in ductal closure but there is limited information on long-term safety.There is some evidence to support the use of paracetamol in late treatment of PDA after failure of previous NSAID therapy, although the efficacy in achieving ductal closure was only 15%.

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Introduction

The ductus arteriosus is an essential anatomic conduit in the fetus, connecting the pulmonary artery to the aorta allowing much of the right ventricular blood to bypass the unexpanded lungs. After birth, the DA closes and becomes the ligamentum arteriosum **(1,2)**.

Functional closure of the ductus arteriosus usually occurs by about 48 hours of life in healthy, full-term infants. If ductus arteriosus fails to close spontaneously, it is termed patent ductus arteriosus (PDA), which leads to left-to-right shunting from the aorta to the pulmonary artery, and a subsequent increase of left ventricular preload **(3, 4)**.

Patent ductus arteriosus accounts for 5–10% of all congenital heart diseases **(5)**. It occurs more commonly in premature infants, where 8 out of 1000 premature infants have PDA compared to 2 out of 1000 term infants. It is more common in females with a female to male ratio of 2: 1 However, true incidence may be as high as 1 in 500 term newborns because many cases with silent PDA are discovered incidentally by echocardiography done for other purposes **(6)**.

Investigations for PDA diagnosis:

ECG:

In patients with moderate or large shunts, the ECG may demonstrate sinus tachycardia or atrial fibrillation, LVH and left atrial enlargement. In

patients with smaller shunts, the ECG is often completely normal. In the patient with a large ductus arteriosus and elevated pulmonary artery pressure, signs of right atrial enlargement and biventricular hypertrophy are frequently present **(7)**.

Chest X-ray:

Depending on the amount of ductal shunting, the chest radiograph may be completely normal in small shunts or it may show cardiomegaly of varying degrees with enlargement of LA and LV with increased pulmonary vascular markings in moderate to large shunts. The main pulmonary artery is frequently enlarged, and particularly in older adults with pulmonary hypertension, calcification of the ductus may be evident **(7)**.

Laboratory findings:

Circulating B-type natriuretic peptide, secreted by ventricles under hemodynamic stress or CHF, can be a sensitive and specific indicator of hemodynamically significant PDA that requires treatment. Levels between 70 and 100 pg/mL have been used to diagnose symptomatic PDA **(8)**.

Echocardiography:

Echocardiography is the gold standard to confirm the diagnosis and to characterize a PDA. In conjunction with the clinical information, the echocardiogram is often useful in classifying the PDA as small, moderate or large. In addition to evaluating the ductus arteriosus, the echocardiogram is used to identify and evaluate other associated cardiac defects **(8)**.

M-mode echocardiography is used to measure the cardiac chamber sizes and quantitate left ventricular systolic function. In a patient with a small PDA, chamber sizes are usually normal, although mild left atrial and/or left ventricular enlargement may be present. In a patient with a moderate or large PDA, the LA and LV are enlarged **(7)**.

Two-dimensional imaging demonstrates the geometry of the ductus and its size can be assessed in a high parasternal view or in a suprasternal notch view **(9)**.

Color Doppler is a very sensitive modality in detecting the presence of a PDA and is frequently used to estimate the degree of ductal shunting. Even an extremely tiny PDA can be detected by a color flow signal entering the pulmonary artery near the origin of the left pulmonary artery. In patients with high pulmonary vascular resistance and PDA, with low velocity or right-to-left flow, the PDA may be very difficult to demonstrate with color flow Doppler, even if it is large. Findings such as septal flattening, unexplained right ventricular hypertrophy and high-velocity pulmonary regurgitation should warrant a thorough investigation for a PDA **(7)**.

Contrast echocardiography may be helpful in this setting; intravenous injection of agitated saline leads to microbubbles in the descending aorta (from ductal right-to-left shunting) but not in the ascending aorta **(7)**.

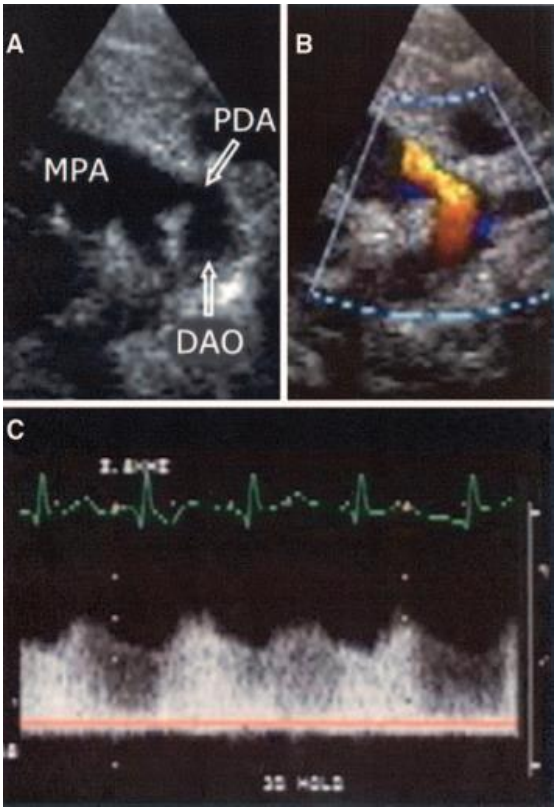

Figure (1): Echocardiogram study demonstrating PDA. A, two-dimensional image of a PDA as seen in a high parasternal short axis view. DAO indicates descending aorta; MPA, main pulmonary artery. B, Color Doppler image in a similar view shows left-to-right shunting through the ductus. C, Spectral Doppler profile of continuous left-to-right ductal flow [3].

Treatment of PDA in term infants and children:

It includes surgical and nonsurgical closure of the PDA. Unlike in premature infants with PDAs, indomethacin is ineffective in term infants and should not be used **(9)**.

1- Medical treatment:

Patients with a symptomatic PDA will usually improve after treatment with diuretics and digoxin to treat their congestive heart failure. These patients may also benefit from treatment with an angiotensin- converting enzyme inhibitor to reduce afterload **(8)**.

Medical therapy for CHF is typically short term until the PDA can be closed by catheterization, however, patients with significant symptoms and cardiomegaly may require long-term treatment **(8)**.

Prophylaxis for infective endocarditis is recommended for all patients with PDA until 6 months after closure **(8)**.

Patients with PDA and pulmonary vascular disease may benefit from pulmonary vasodilating agents such as chronic oxygen, PGI2, calcium channel blockers, endothelin antagonists, and phosphodiesterase type 5 inhibitors, although there are no systematic studies on the benefit of these agents in patients with PDAs and high pulmonary vascular resistance. PDA closure is reasonable for patients with PAH with a net left-right shunt. PDA closure is not recommended for patients with PAH and a net right-left shunt **(8)**.

2- Nonsurgical closure of the PDA (transcatheter closure):

Before the invention of catheterization therapy, surgical closure was recommended as the main routine treatment. As minimally invasive technology has developed, using a catheter for interventional treatment has emerged as a trend. It was demonstrated that transcatheter closure of PDA using conical Ivalon plug in a 17-year-old male patient, then it has become the preferred method of treatment for children beyond the neonatal period and efficacy of this method which is performed using various devices and coils has been confirmed in pediatric and adult patients, also closure with device has been firstly recommended in current guidelines especially for cases with isolated PDA **(10)**.

It wa reported that use of Gianturco coils for transcatheter closure of PDA, transcatheter coil occlusion quickly became a widely used technique for closure of the small to moderate patent ductus. Subsequently, newer devices and techniques have been developed such that moderate and large patent ductus are usually amenable to occlusion by transcatheter techniques. In addition, the development of less invasive surgical techniques have paralleled the development of transcatheter techniques **(7)**.

Indications for closure of PDA:

1. Closure of PDA is definitely indicated in patients with hemodynamically significant PDA with CHF, failure to thrive, pulmonary overcirculation, or enlargement of the LA and LV **(9)**.
2. It is reasonable to close a small PDA when the murmur of PDA is audible by standard auscultation techniques **(9)**.
3. There is controversy related to occlusion of so-called silent ductus. There are few data on the benefits of occluding the silent ductus because of lack of significant endothelial damage to cause endocarditis **(9)**.
4. Ductal closure is contraindicated in patients with Eisenmenger's syndrome or pulmonary vascular obstructive disease. The response of PVR to balloon occlusion or pulmonary vasodilators (e.g., oxygen or nitric oxide) is

tested in the cardiac catheterization laboratory. If a good response is obtained, closure is advised. If the response is poor or equivocal, closure may not be recommended **(9)**.

Technique and devices:

The basic technique is to advance a catheter or delivery sheath across the ductus arteriosus from either the pulmonary artery or the aorta and position a closure device in the ductus to occlude it **(7)**. In most cases, Small ductus (<3 mm in diameter) are closed by various kinds of coils. For larger PDA but smaller than 12 mm in diameter, specialized devices, such as the Amplatzer duct occluder, are available for catheter-based closure **(9)**.

Stainless steel coils have become the standard device for closure of PDA for all children with ducts smaller than 3 mm in diameter. In optimal candidates for the device, the ductus is 2.5 mm in size, but the use of multiple coils can close a ductus up to 5 mm. A retrograde approach is used from the femoral artery or antegrade approach through the femoral vein and pulmonary artery. The residual shunt rate is 5% to 15% at 12 months of follow-up. Overall, the procedure has 97% or greater success with zero mortality **(9, 11)**.

The standard, nondetachable Gianturco coils, occasionally migrated or assumed unacceptable positions, so several techniques were developed to stabilize the coils during delivery. In addition, detachable coils are now readily available, which allow the assessment of adequate positioning before release. In contrast to Gianturco coils, which were designed for occlusion of vascular structures other than the patent ductus, the Nit-Occlud coil occlusion system was specifically designed for closure of the PDA. The coil has a biconical shape that is more suitable to the conical shape of most patent ductus than the cylindrical Gianturco coils **(7)**.

For larger PDA but smaller than 12 mm in diameter, specialized devices, such as the Amplatzer duct occlude, are available for catheter-based closure. The devices are implanted antegrade from the femoral vein. Although original recommendations from the manufacturer exclude patients who weigh less than 6 kg, successful use in infants as small as 2.5 kg has been reported **(9)**.

The Amplatzer duct occluder is made of nitinol wire woven into a mesh in the configuration of a mushroom-shaped plug, and it has a detachable cable, which allows easy repositioning or retrieval if necessary. For some patients with larger type B (short) ductus, the Amplatzer septal occluder device, a Dacron fiber–filled nitinol mesh with 2 disks connected by a short waist, may be effective. In addition to the devices described above, newer devices and modifications are in the process of being developed and tested. The Amplatzer duct occluder has been modified such that the retention skirt has an angle and concavity that allows it to fit better at the aortic end, and this device is currently under investigation **(7, 12)**.

Given the numerous variations of PDA configuration and size, it is apparent that any individual device will not be optimal for closure of all patent ductus. The availability of a variety of devices and techniques enhances the capability to close the vast majority of patent ductus with catheter-based techniques. Results of transcatheter occlusion of PDA have been excellent with minimal complications and zero mortality. Complete closure rates at follow-up generally exceed 90% to 95% in most studies. As a result of device modifications, evolution of new techniques, and increased operator skill, success rates for complete closure have improved significantly over time. Even when a small residual shunt is detected at follow-up, complete occlusion can usually be achieved by delivery of a single small additional coil **(7)**.

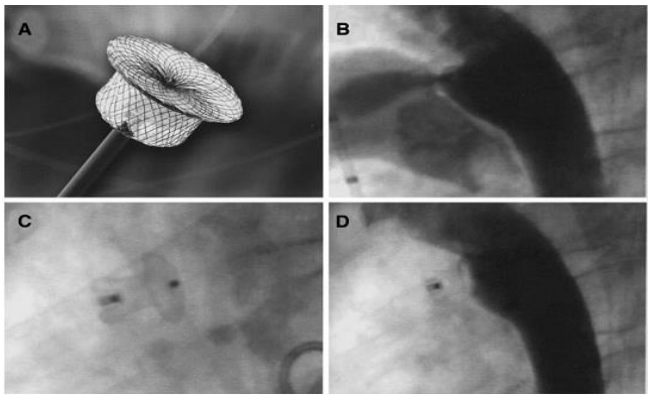

Figure (2): Example of PDA occlusion with an Amplatzer duct occluder device. A, image of an Amplatzer duct occlude device. B through D, lateral angiograms demonstrating closure of a PDA with an Amplatzer duct occluder device [(3)].

Advantages of transcatheter closure of PDA:

The advantages of nonsurgical closure of the ductus include no need for general anesthesia, shorter hospital stay and convalescent period, and elimination of a thoracotomy scar **(9)**.

Potential complications of the transcatheter closure of PDA:

Serious complications of transcatheter closure of the PDA are rare. The most common complication is device embolization, which was relatively common early in the experience with coils. Embolized coils are usually retrieved, but even in cases in which they cannot be retrieved, adverse consequences are rare. Other complications are flow disturbance in the proximal left pulmonary artery or descending aorta from a protruding device, hemolysis from high-velocity residual shunting, femoral artery or vein thrombosis related to vascular access, and infection **(7, 13)**.

Surgical closure of PDA:

Although generally associated with greater pain and morbidity than transcatheter methods, surgical ligation and surgical division are safe and effective procedures and remains the treatment of choice for the rare very large ductus and are reserved for patients in whom a nonsurgical closure technique is not considered applicable. Rarely, a large, window-type PDA may have insufficient length to permit ligation, and the appropriate surgical procedure is patch closure on cardiopulmonary bypass. Complete closure rates of surgical ligation (often accompanied by division of the ductus) in published reports range from 94% to 100%, with 0% to 2% mortality **(7)**.

Procedure:

a. Ligation and division through left posterolateral thoracotomy without cardiopulmonary bypass is the standard procedure **(14, 15)**.

b. The technique of video-assisted thoracoscopic surgery (VATS) clip ligation has become the standard of care for surgical management of ductus with adequate length (to allow safe ligation), which is performed through three small ports in the fourth intercostal space **(9)**.

Complications:

Complications are rare. Injury to the recurrent laryngeal nerve (hoarseness), the left phrenic nerve (paralysis of the left hemidiaphragm), or the thoracic duct (chylothorax) is possible **(16, 17)**. Recanalization (reopening) of the ductus is possible, although rare, occurring after ligation alone (without division) **(10)**. Other complications include bleeding, pneumothorax, infection, and rarely, ligation of the left pulmonary artery or aorta. Morbidity, cost and hospital stay have been decreased with use of

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transaxillary muscle-sparing thoracotomy and by the technique of video-assisted thoracoscopic ligation of the PDA **(7, 18).**

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