ABSTRACT: Transcatheter closure of a patent ductus arteriosus (PDA) is a well-established technique that may occasionally be complicated by severe thrombocytopenia. We report herein 6 cases of PDA in which circulating platelet counts were notably reduced within 18-48 hours following the procedure. A number of interventions, including blood-pressure control, protection against hemorrhage, and eradication of residual flow, were performed. Platelet counts in all patients were restored to preprocedural levels through intravenous infusion of dexamethasone and human gamma globulin.

Key words: patent ductus arteriosus, transcatheter, occlusion, thrombocytopenia

Closure of a patent ductus arteriosus (PDA) is indicated to prevent bacterial endarteritis, congestive heart failure, and/or pulmonary vascular disease. Percutaneous transcatheter closure of a patent arterial duct was first performed in 1967 by Porstmann et al, and the technique has been widely used since the early 1990s. Nowadays, transcatheter closure of a PDA using Gianturco coils and mushroom occlusive devices has become the treatment of choice at many institutions, since it is safe as well as cost effective and offers considerable advantages over surgical ligation. Moreover, recent advances in device technology allow closure of virtually all PDAs, regardless of size or configuration, except in premature infants. Despite these advances, transcatheter closure of a PDA can be associated with rare complications. We report herein 6 cases of severe thrombocytopenia complication following transcatheter occlusion of a PDA.

Case Report. Two male and 4 female patients (including 2 infants, 3 children, and 1 adult) were referred to our institute for percutaneous transcatheter closure of a PDA. The age of the patients ranged from 16 months to 28 years and body weight ranged from 8.5 kg to 38 kg (Table 1). All patients had experienced fatigue and shortness of breath on exertion during the previous year.

Clinical examination of all cases revealed either a grade 2-4/6 continuous murmur (4 cases) or a 2/6 systole murmur (2 cases) in the second and third interspaces to the left of the sternum. A chest x-ray showed mild-to-severe cardiomegaly in all cases, with left ventricular or double ventricular enlargement. Electrocardiographic data were either normal or indicative of ventricular volume overload (Table 1). The echocardiograms of all patients revealed a PDA with a large shunt, dilation of the main pulmonary artery, and a moderately enlarged left ventricle and left atrium.

After obtaining informed consent from all patients or guardians, a standard right and retrograde left heart catheterization was performed under general anesthesia. A bolus of heparin calcium (70 U/kg) was administered by intravenous injection. Cefazolin was administered during the procedure and twice afterward at spaced
intervals. Main pulmonary artery systolic pressure (PASP), pulmonary artery mean pressure (PAMP), aortic systolic pressure (ASP), and aortic mean pressure (AMP) ranged from 85-128, 60-92, 120-152, and 83-99 mm Hg, respectively. No pressure gradient was identified around the aortic arch, and the calculated pulmonary-to-systemic flow ratio (Qp:Qs) ranged from 2.0:1 to 3.0:1. Angiography of all cases revealed large PDAs (3 Krichenko type C and 3 Krichenko type A) with diameters at the aortic and pulmonary ends of 7.2-23.0 mm and 5.0-17 mm, respectively, and a length of 6.0-18.0 mm (Table 1).

In Case 1, a 14/12 mm Amplatzer ductal occluder (ADO; St Jude Medical) was selected (Figures 1A and 1B), while a 16 mm muscular ventricular septal defect (VSD) occluder (SHSMA Medical) was used in Case 5 (Figures 2A and 2B). The ADO II is used for occlusion of PDA with diameter less than 5.0 mm, and may be unsuitable for those with diameter more than 5.0 mm in our cases. In all other cases, a PDA occluder or VSD occluder was selected (Table 1). Immediately following the procedure, PASP and PAMP decreased to 32-72 mm Hg and 21-45 mm Hg, respectively, while ASP and AMP were elevated to 104-164 mm Hg and 75-113 mm Hg, respectively. Ten minutes after intravenous administration of sodium nitroprusside, PASP, PAMP, ASP, and AMP decreased to 24-40, 16-23, 103-112, and 79-91 mm Hg, respectively. An aortogram, performed 10 minutes after delivery of the occluders, revealed what was believed to be mild residual flow past the occlusion of the PDA.

On the day following the procedure, blood tests revealed a reduction in circulating platelet count from 118,000-302,000/µL to 36,000-191,000/µL in all cases (Figure 3), and normal serum hemoglobin levels. No spontaneous bleeding occurred, and no red blood cell destruction or hemoglobinuria were observed after the procedure. Urinalysis, international normalized ratio, blood creatinine, urea nitrogen, total and indirect hemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AKP), platelet-associated antibody immunoglobulin (IgG), and blood antithrombin activity were all found to be nor-

![Figure 2. Aortogram pre- and post-closure of patent ductus arteriosus (PDA). (A) Large C-type PDA. (B) Pulmonary artery clearly seen after aortogram, demonstrating mild residual flow past the occlusion of the PDA.](image)

![Figure 3. Circulating platelet counts before and after closure of patent ductus arteriosus (PDA), demonstrating a ‘U’-type curve. The circulating platelets decreased to a nadir on Day 4-6 after occlusion of PDA, and recovered to normal levels by Day 8-13.](image)
Platelet factor 4 (PF4)-heparin antibody was negative and no residual shunt was observed by echocardiogram.

The number of circulating platelets reached a nadir of 5,000-29,000/µL on days 4-6 after occlusion of the PDA. Desmethylsone sodium phosphate (5 mg, qd) was administered for 3-5 days and human IgG (Sansheng Corporation; 2.5 g, qd) was administered for 2-3 days in all cases. In Case 4, recombinant human thrombopoietin (Sansheng Corporation; 4800 U, qd) was administered for 3 days. Circulating platelet counts recovered to normal levels (104,000-140,000/µL) on day 8-13 (Figure 3), and remained normal over a follow-up period lasting from 2 months to 2 years.

Discussion. Transcatheter PDA closure is a safe and effective treatment. Due to anatomical variations and differences in size, a single device will always be limited as a total solution for PDA closure. Today, the devices most commonly used to perform the procedure are coils and the mushroom PDA device. The Amplatzer muscular VSD occluder currently remains an investigational product, but has been used to close large PDAs associated with significant pulmonary hypertension. In our experience, the rationale for choosing an occluder is that the device’s smallest diameter is 4-6 mm larger than the smallest ductal diameter in infants and children, and it is 2-4 mm larger in adults because of the lower distensibility of ductal tissue in adults than that in infants and children. A muscular VSD occluder is better suitable for a large Krichenko type-C PDA with a large diameter (>10 mm). An unsuitable device may cause iatrogenic coarctation of the aorta.

Major complications of transcatheter PDA closure include hemolysis after incomplete closure, device embolization to a systemic or pulmonary artery, infection, left pulmonary artery obstruction, thoracic aorta obstruction, femoral arteriovenous fistula formation, and heparin-induced thrombocytopenia (HIT). Thrombocytopenia associated with transcatheter intervention is generally thought to result from HIT, a condition that presents in two forms. Type-1 HIT is a mild, transient decrease in platelet count that occurs during the first few days of heparin exposure due to platelet agglutination. In Type-1 HIT, the platelet count returns to normal levels while heparin treatment is continued. Type-2 HIT is an antibody-mediated thrombocytopenia that is associated with a high risk of thrombosis. Type-2 HIT is more common in adults, but may also occur in children. Onset of thrombocytopenia in this form tends to occur 5 to 10 days after heparin initiation. Antibodies may also activate platelets, further increasing the risk of thrombosis.

HIT is diagnosed clinically. Serologic testing for PF4-heparin antibodies is recommended when the clinical suspicion of HIT is high or intermediate because negative results on serologic testing have a high negative predictive value in these cases and suggest an alternative diagnosis. In our case series, PF4-heparin antibodies were negative in all cases. Moreover, thrombocytopenia occurred within 15 to 48 hours postprocedure in all of our patients, and platelet counts decreased dramatically. These observations further weaken a diagnosis of HIT.

In the literature, complications of thrombocytopenia were due to intravascular mechanical hemolysis following incomplete PDA closure, of which the main clinical characteristics were composed of mechanical damage of red blood cell, a significant decrease in serum hemoglobin, red discoloration of the patient’s urine, hemoglobinuria with red blood cells, and residual shunt observed by echocardiogram complicated with thrombocytopenia. To our knowledge, there have been no reports of complications due to simple thrombocytopenia.

At our institute, 5401 patients underwent congenital and acquired heart disease occlusion (including 1928 PDAs, 1999 atrial septal defects [ASDs], 1415 perimembranous VSDs, 20 muscular VSDs, 14 ventricular septal ruptures, and 25 aneurysm of Valsalva sinus ruptures) between March 1998 and October 2011. The cases presented herein were selected because of their large PDA size. PDA occlusion was attempted using a VSD occluder in 3 patients and a mushroom PDA occluder in the other 3 patients.

All cases were large PDAs complicated by pulmonary artery hypertension, and had mild residual flow from the middle of the device as shown by aortogram performed 10 minutes after occlusion. Six of the 1928 cases (3.11‰) who underwent PDA occlusion developed thrombocytopenia. Thrombocytopenia occurred in patients who underwent PDA occlusion only, with those who underwent ASD or VSD closures not experiencing this complication. This suggests that anaphylaxis was not the cause of the thrombocytopenia.

The formation of stable thromboses in occluders consumes a number of platelets and contributes to the development of thrombocytopenia. The mushroom duct occluder and muscular VSD occluder are formed from 72-gauge nitinol, incorporating a fabric layer. The mean aperture of the polyester fiber fabric is approximately 160 µm, while the diameter of a human platelet is 2-3 µm. If there is no residual flow after PDA occlusion, platelets aggregate faster in the metal and fabric meshes, triggering the extrinsic coagulation system to form a stable thrombus and decrease the number of platelets consumed.

The blood lifespan of human platelets is 7-14 days, and approximately 10% of platelets are renewed every day. The equilibrium of platelet renewal and consumption can be maintained in the absence of continued platelet consumption. When a large occluder is used and continuous residual flow exists, platelets cannot adhere to the occluder and the adhered platelets are destroyed due to the high flow velocity. Moreover, platelet aggregation in a large occluder also consumes a number of platelets. If the number of platelets consumed exceeds the number renewed, the circulating platelet count decreases.

In our group, we found that the bigger the diameter of the occluder, the greater the prevalence of thrombocytopenia.
nia. However, although some ASD occluders had a diameter exceeding 30 mm, larger than the PDA occluder used in our group, no apparent decrease in platelet count occurred in the ASD patients. This may be explained by the fact that the very small pressure gradient between the left and right atria allowed platelets adhered in the occluder not to be destroyed by blood flow, resulting in no ongoing consumption of platelets. Moreover, despite the high pressure gradient between the left and right ventricle, none of the 1415 VSD patients had thrombocytopenia. We considered that this might have occurred because the diameter of the VSD occluder was smaller than that of the PDA occluder. Fewer platelets adhered to the relatively small VSD occluder, and the thrombus was formed in the device before the platelet counts apparently decreased. The PDA occluder is columnar and incorporates more integrated fabric, allowing a greater number of platelets to adhere. It is difficult for stable thrombi to form because of the high-velocity blood flow through the occluder. As a result, a large number of platelets are consumed.

The general approach to the management of a patient with significant thrombocytopenia post PDA occlusion consists of blood-pressure control, protection against hemorrhage, and eradication of residual flows. This is accomplished by correcting thrombocytopenia through platelet transfusions, inhibiting presumed immunological reaction by glucocorticoids and human immunoglobulin administration, and precise control of blood pressure through sodium nitroprusside administration.

**Conclusion.** Caution should be taken in the early period following large PDA occluder implantation, especially in patients who have a residual flow. In general, when thrombocytopenia occurs post PDA occlusion, conservative medical treatment can achieve satisfactory effect. Platelet transfusions may be required in some patients, and surgical operations should be applied if purely medical treatments fail.
References

12. Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombo-