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Catheter Interventions for Kawasaki Disease: Current Concepts and Future Directions

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ABSTRACT

During the past 15 years, clinical experience with catheter interventional treatment in patients with Kawasaki disease, including balloon angioplasty, stent implantation, rotational ablation, and transluminal coronary revascularization, has been gradually increasing. Because the coronary artery lesions in Kawasaki disease involve severe calcifications, the indications or catheter intervention techniques have not been established for adult patients with Kawasaki disease. Satisfactory acute results for coronary balloon angioplasty have been obtained in patients with a relatively short interval from the onset of disease, especially within 6 years; however, the incidence of restenosis after angioplasty is still high. Rotational ablation may be the most appropriate catheter intervention technique for patients with Kawasaki disease. The advantage of rotational ablation is the high success rate, even in patients with calcified coronary artery stenosis. Stent implantation requires larger arterial access and is not possible in younger children. Care should be paid to the detection of newly-formed aneurysms, as the formation of new aneurysms is associated with the use of additional balloon angioplasty using high pressure balloon inflation. Anticoagulation or anti-platelet regimens are essential for long-term management. Coronary intervention in Kawasaki disease requires special techniques and knowledge of cardiovascular involvement. The procedure should be managed under the close collaboration between pediatric cardiologists and coronary interventional cardiologists. **(Korean Circ J 2011;41:53-57)**

KEY WORDS: Kawasaki disease; Angioplasty balloon; Coronary arteries.

Introduction

Coronary artery involvement is the most important complication of Kawasaki disease (KD), and may cause significant ischemic heart disease in children. Acute myocardial infarction due to thrombus occlusion of a coronary aneurysm is the most serious complication in KD. After the introduction of high-dose gamma globulin, the incidence of coronary aneurysm formation has declined dramatically. Between 30% and 50% of such aneurysms regress within the first 2 years; however, 3-5% of patients have chronic coronary aneurysms which may become stenotic and obstructive, thus leading to myocardial infarction. In Japan, >8,000 children have been diagnosed with KD annually during the past 10 years. Thus, nearly 400 children per year develop coronary aneurysms from KD. Coronary artery bypass surgery (CABG) has been performed for ischemic heart disease caused by KD; however, long-term coronary graft patency is not satisfactory, especially in venous grafts and patients <8 years of age. Therefore, catheter intervention has its role in KD related to coronary artery disease (CAD).

During the past 15 years, clinical experience with the following catheter interventional treatments in patients with KD has been gradually increasing:[1] balloon angioplasty;[2][3] stent implantation;[4][5] rotational ablation;[6][7] and transluminal coronary revascularization.[8] However, the experiences in KD are limited compared to coronary intervention in adults, which have provided satisfactory therapeutic results. The coronary artery stenosis in patients with KD commonly involves severe calcifications, in contrast with adult coronary artery lesions, which primarily consist of atherosclerosis.[9][10] Therefore, the indication for catheter intervention in adult patients cannot be directly applied to patients with KD, most of whom are in

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the pediatric population.[11] Indeed, the fundamental therapeutic regimen for patients with ischemic heart disease after KD is CABG; however, the long-term coronary graft patency is not satisfactory, especially in venous grafts or patients <8 years of age.[12][13] Furthermore, the indications for catheter intervention in patients with KD have not been established, and the long-term prognosis after catheter intervention remains unclear.[1][11]

Several types of catheter interventions for the treatment of KD have been reported. Although these preliminary reports have demonstrated the efficacy of each procedure, the studies have been limited and no prospective studies have been performed. Although the use of percutaneous coronary rotational ablation (PTCRA) is still limited, this procedure may be the most appropriate catheter intervention for patients with KD. The advantage of PTCRA is the high success rate, even in patients with calcified coronary artery stenoses.[6][7] Care should be paid to the detection of newly-formed aneurysms, as the formation of new aneurysms is associated with the use of additional coronary balloon angioplasty using high pressure balloon inflations. The etiology of new aneurysms is likely intimal dissection caused by balloon angioplasty rather than rotational ablation. The advantages of this procedure include the high vascular patency rates in patients with segmental or relatively long stenoses, and the prevention of new aneurysm formation after percutaneous transluminal coronary balloon angioplasty (PTCA). As with PTCRA, stent implantation requires larger arterial access and is not possible in younger children.

Indications for Catheter Intervention

The following patient conditions for catheter intervention should be considered.[14]

1) Patients presenting with ischemic symptoms.

2) Patients presenting with no ischemic symptom, but shown to have ischemic findings detected by stress testing (dipyridamole stress myocardial perfusion scan or dobutamine stress echocardiography).

3) Patients with no ischemic findings detected by stress testing, but >75% of stenotic lesions in the left anterior descending coronary artery, possibly causing sudden cardiac death by obstruction. In such cases, the indication for catheter intervention can be considered. Other therapeutic options, including surgical therapy or observation with medications, should also be discussed.

4) Patients with severe left ventricular dysfunction are not candidates for catheter intervention, and other options, including CABG, should be considered.

The indications by lesion site are as follows:

1) severe stenotic lesions (>75%);

2) localized lesions (contraindication for cases with multiple vessel lesions);

3) no ostial lesions; and

4) no long segmental lesions.

Types of Procedures

Percutaneous transluminal coronary balloon angioplasty

PTCA is only useful for stenotic lesions with mild calcifications or the absence of calcifications within 6 years of disease onset.[2] Thus, satisfactory acute results for PTCA have been obtained in patients with a relatively short interval between the onset of disease and PTCA within 6 years after onset. However, the success rate declined to 60% if the interval from the onset of disease to the time of PTCA was >10 years. Pathologic examinations at the time of autopsies have demonstrated marked intimal thickening secondary to arteritis at the sites of aneurysms and stenoses. Multiple calcifications have also been detected in the arterial wall.[15] Calcified lesions are observed beginning approximately 5 years after onset. The underlying obstacle to successful PTCA is reduced compliance of the arterial wall. In the setting of reduced compliance, alternative procedures, such as rotational ablation, should be attempted.

The incidence of restenosis after PTCA is high.[1] In fact, approximately, 25% of patients develop restenosis or occlusion. The mechanism responsible for restenosis is the same as that responsible for failure of adequate balloon dilation. Coronary arteries with thick intimal hyperplasia probably recoil easily, even if the stenotic vessel has been dilated sufficiently. Stent implantation may prevent the occurrence of restenosis in this situation.

The development of new coronary aneurysms after PTCA is a significant clinical concern. The mechanism responsible for this phenomenon is unclear, however intimal and/or medial dissection due to high-pressure balloon inflation could play a role. In a previous report the maximum balloon pressure in patients with new aneurysms was >10 atmospheres.[1] Although an increase in aneurysm diameter or aneurysmal rupture has not been reported, more rigorous trials are necessary to determine the risk of this complication. Thus, the maximum balloon pressure is recommended to be <8-10 atmosphere at the time of PTCA in the pediatric population. Stiff coronary artery lesions which require higher balloon pressure (>10 atmospheres), rotational ablation or CABG surgery is advisable as an alternative procedure. Additionally, when PTCA is defensively performed in young children, a short balloon length should be selected.

Stent implantation

Use of stent implantation for KD is limited; however, acute results with stent implantation have been excellent. Because this procedure relies on balloon dilation, the limitations are similar to the limitations for PTCA. The advantages of stent

implantation include high vascular patency rates in patients with segmental or relatively long stenoses, and the prevention of new aneurysm formation after PTCA.[8)11)] As with rotational ablation, stent implantation requires larger arterial access and is not possible in younger children. Stent implantation is useful for old children (>13 years) in whom calcifications are mild and the stent can be implanted in coronary arteries. Stent implantation is also effective in patients in whom the coronary blood flow is whirling inside of giant aneurysms because the blood vessel diameter can be extended as large as the stent diameter compared to other procedures. The incidence of new aneurysms is lower following stent implantation than PTCA alone, even if a higher balloon pressure is applied. Maximum balloon pressure is recommended not to exceed 14 atmospheres to avoid the formation of neoaneurysms. Stent implantation is ineffective in cases with severe calcifications. Heparin should be infused at 800-1,000 U/h. The activated clotting time is maintained at 200 seconds or more. Anticoagulation therapy with aspirin and clopidogrel is recommended for >2 months after the procedure. The long-term results of this procedure in patients with KD should be clarified in further studies.

Rotational ablation

PTCRA consists of an abrasive tiny diamond-coated burr that removes the lesion with rotation at 200,000 rpm and allows the lumen to dilate. Rotational ablation is also effective in cases with severe calcifications. Excellent acute results for PTCRA were observed in previous studies.[6)7)] Although use of this procedure is limited, PTCRA may be the most appropriate catheter intervention for KD. The advantage of PTCRA is the high success rate, even in patients with calcified coronary artery stenoses. Care should be paid to the detection of new aneurysm formation, as the formation of new aneurysms is associated with the use of additional PTCA using high-pressure balloon inflation. The etiology of new aneurysms is likely intimal dissection caused by balloon angioplasty and not rotational ablation. Indeed, the findings based on intravascular ultrasound imaging support this speculation.[6)] Therefore, balloon dilation after PTCRA should be avoided. If balloon dilation is required (i.e., for persistent residual stenosis) after PTCRA, the balloon pressure should be kept low. The limitation of this procedure is the need for larger arterial access for the metal burr. For this reason, this procedure can only be performed in older patients. Using this procedure, the stenotic area can be dilated up to 2.5 mm. Combination of rotational ablation and stent implantation may facilitate a further enlargement increase the diameter of the coronary artery diameter. As with stent implantation, heparin infusion (800-1,000 U/hour) is critical during the procedure. The activated clotting time should be maintained at ≥200 seconds. Anti-platelet medication should be continued at least 2 months after the procedure.

Percutaneous transluminal coronary revascularization

Acute myocardial infarction most frequently occurs within 2 years of the onset of KD and is mainly caused by fresh thrombi.[9)] PTCR and intravenous thrombolysis in this situation are thought to be significant in the prevention and therapy of myocardial infarction.[8)] In particular, frequent and careful observation with echocardiography is required in cases, such as giant coronary aneurysms, which have a high risk for thrombus formation. In patients undergoing percutaneous transluminal coronary revascularization (PTCR), 25,000 U/kg of tissue plasminogen activator (t-PA) is administered. Injection of thrombolytic agents directly into the coronary artery and intravenous thrombolysis occasionally cause cerebral hemorrhage. Repeated doses of the thrombolytic agents should be carefully performed in pediatric patients who are predisposed to hemorrhage. After PTCR, 100 U/kg/hour of heparin is intravenously infused for 12 hours. Thereafter, a small oral dose of aspirin or warfarin is administered to prevent thrombus formation. Because t-PA is injected intravenously, an intravenous infusion of t-PA (250,000 U/kg) is recommended prior to hospitalization in cases of acute myocardial infarction in pediatric patients with KD. However, it is necessary to take careful precautions against cerebral hemorrhage and arrhythmias caused by the systemic administration of t-PA. PTCR or intravenous thrombolysis in patients with acute myocardial infarction is generally effective only within 6 hours after onset. PTCR or intravenous thrombolysis may be indicated for fresh thrombi in giant coronary aneurysms detected by serial echocardiography. The success rate for re-canalization using thrombolytic agents is low in cases of asymptomatic myocardial infarctions secondary to chronic obstruction with thrombi.

Long-Term Outcome After Intervention

Eighty-eight patients (71 males and 17 females), who developed coronary stenotic lesions caused by KD were treated with catheter interventions in 9 institutions between January 1993 and June 2002. At the time of the intervention, the subjects ranged in age from 11 months to 27 years (mean age, 14±5.5 years), and the interval between diagnosis of KD and intervention was 137 days to 25 years (mean interval, 11.8±6.3 years). Catheter intervention was considered successful when the degree of stenosis (diameter) was <50% of the degree of stenosis before the procedure 9. Restenosis was present when the minimal luminal diameter was reduced by >50%, as confirmed by angiography. New coronary aneurysms were defined as aneurysmal coronary enlargement at the same site of intervention observed at the time of follow-up angiography. A total of 100 catheter interventions were performed on the 88 patients. The mean follow-up period after catheter intervention was 3.7±3.6 years (range, 31 days to 7.1 years). The procedures were

divided into three groups: PTCA (n=21); PTCRA (n=68); and stent implantation (n=11). Prior to stent deployment, 6 and 5 patients underwent PTCA and PTRCA, respectively, at the same time. The mean age at onset, intervention, and follow-up period are listed in Table 1. The age at intervention in the PTCRA and stent implantation groups was significantly older than the PTCA group (p=0.043).

The main long-term results regarding restenosis, neoaneurysms, re-intervention, conversion to CABG, and complications are listed in Table 2. The incidence of restenosis was higher in the PTCA group (24%) than the PTCRA (17%) and stent insertion groups (9%). The incidence of neoaneurysm formation was also higher in the PTCA group (7.4%) than the PTCRA group (6.3%); no neoaneurysms were reported in the stent bimplantation group. The re-intervention rate was highest in the PTCRA group (12.5%) and lowest in the stent implantation group (0%). The PTCA group had the highest rate of conversion to CABG and the highest complication rate. The event-free survival curve is demonstrated in Fig. 1, which showed 1-year event-free ratios of 66.7%, 89.9%, and 90.9% for the PTCA, PTCRA, and stent implantation groups, respectively. The 5-year event-free ratios were 66.7%, 69.1%, and 90.9% for each group.

In the PTCA group, 5 lesions developed restenoses. We compared these lesions with the other 16 lesions with respect to the age at intervention, degree of stenosis, maximal balloon size, and maximal pressure. We showed that high-pressure inflation tended to cause restenosis (p<0.05), as shown in Table 3. In the PTCRA group, 12 lesions had restenoses and the associated risk factor was the smaller Burr size, as shown in Table 4.

Table 1. Patient profile

	PTCA (n=21)	PTCRA (n=68)	Stent (n=11)
Age at onset (years)	2.9±1.5	2.4±2.2	2.5±2.8
Age at intervention (years)	7.4±5.2	15.4±4.5*	16.1±2.3*
Follow-up (years)	4.2±2.6	3.4±4.2	4.0±2.5

*Means p<0.05 compared with the PTCA group. PTCA: percutaneous transluminal coronary balloon angioplasty, PTCRA: percutaneous coronary rotational ablation

Table 2. Main results of interventions

	PTCA (n=21)	PTCRA (n=68)	Stent (n=11)
Restenosis (%)	24	17	9
Neoaneurysm (%)	7.4	6.3	0
Re-intervention (%)	3.7	12.5	0
CABG (%)	18.5	0	9
Complications (%)	14.8	10.4	9

PTCA: percutaneous transluminal coronary balloon angioplasty, PTCRA: percutaneous coronary rotational ablation, CABG: coronary artery bypass surgery

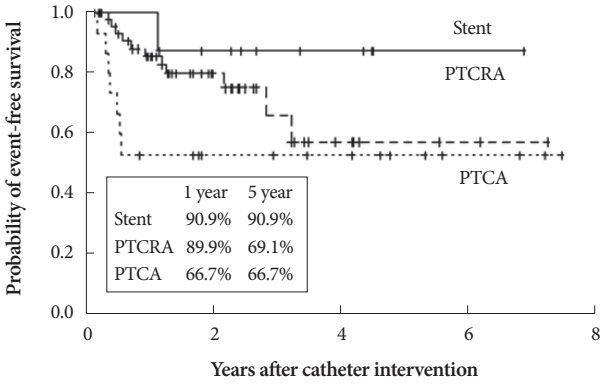

Fig. 1. Event free survival of various interventions.

Role of Intravascular Ultrasound Imaging

The histopathologic features of coronary lesions in patients with KD change with the duration after onset. In particular, calcifications are frequently observed in the area of the coronary stenosis >6 years after onset. The detailed evaluation of the severity and extent of calcifications is extremely important for the optimal selection of suitable therapeutic procedures. Intravascular ultrasound imaging allows detailed structural observation of a coronary artery wall. Specifically, the extent of calcifications can be precisely evaluated.[15] Intravascular ultrasound imaging is desirable to evaluate evaluate the procedure results in detail.

Institute and Back-Up System

All of the above procedures should be performed at select-

Table 3. Risk factors of restenosis after PTCA

	Restenosis (+) (n=5)	Restenosis (-) (n=16)	p
Age at intevention (years)	9.1±4.3	9.7±6.9	NS
Degree of stenosis (%)	94±9	89±12	NS
Maximum balloon size (mm)	2.9±0.5	3.1±0.7	NS
Maximum pressure (atm)	14.3±6.8	8.4±2.0	0.03

PTCA: percutaneous transluminal coronary balloon angioplasty

Table 4. Risk factors of restenosis after PTCRA

	Restenosis (+) (n=12)	Restenosis (-) (n=56)	p
Age at intervention (years)	13.3±1.9	14.8±3.4	NS
Degree of stenosis (%)	89±6	88±9	NS
Burr size (mm)	2.05±0.18	2.22±0.27	0.043

PTCRA: percutaneous coronary rotational ablation

ed institutions with experience in coronary interventional procedures by highly experienced interventional cardiologists. Cooperation between pediatric and adult cardiologists is essential for optimal decision-making in this setting. Patients should be referred by a cardiologist who has fully knowledge of not only the catheter intervention, but also the clinical features and the natural course of the disease.[16] The indications for catheter intervention and appropriate anti-thrombus regimen after interventional catheterization require further clarification in the setting of KD based on the natural history of the coronary artery lesion, especially vascular endothelial function.[17-19]

Recommendations

The current study did not establish guidelines for the use of catheter intervention in patients with KD. However, based on our results, we propose the following recommendations.[20-23] PTCA is effective in many situations, particularly in patients without severe calcifications or in patients with a relatively short interval (<6 years) between the onset of disease and the intervention. Based on recent improvements in balloon catheters, this procedure may be used, even in small children. Therefore, PTCA may become a first-line procedure in younger children with significant coronary artery stenosis. Stent implantation is preferable to PTCA because it may prevent new aneurysm formation and restenosis. In patients older than adolescents, stent implantation should be considered instead of PTCA alone. If patients have severe calcified coronary stenoses, PTCRA may be the only effective treatment. Intravascular ultrasound imaging provides valuable information for the selection of the appropriate interventional procedures and early detection of vascular complications.

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