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Clinical Study Protocol

Feasibility of Repairing Defects Followed by Treatment with Pulmonary Hypertension-specific Drugs (Repair and Treat) in Patients with Pulmonary Hypertension Associated with Atrial Septal Defect: Study Protocol for Interventional Trial

Satoshi Akagi[a]*, Kazufumi Nakamura[a], Teiji Akagi[b], Koji Nakagawa[a], Yoichi Takaya[a], Toshihiro Sarashina[a], Kentaro Ejiri[a], and Hiroshi Ito[a]

[a]*Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science,*
[b]*Cardiac Intensive Care Unit, Okayama University Hospital, Okayama 700–8558, Japan*

A treatment strategy for patients with pulmonary hypertension (PH) and atrial septal defect (ASD) remains unclear. This study was designed to evaluate the effects of initial repair of ASD followed by treatment with PH-specific drugs in patients with PH and ASD. Eligible patients receive transcatheter ASD closure followed by treatment with bosentan and sildenafil. Right heart catheterization is performed at baseline and at 12, 24 and 48 weeks. The primary endpoint is change in pulmonary artery pressure and pulmonary vascular resistance from baseline to follow-up. This study should provide valuable information to establish a therapeutic strategy for PH and ASD.

Key words: pulmonary hypertension, atrial septal defect, repair and treat, transcatheter closure

Pulmonary hypertension (PH) is characterized by the elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) caused by pulmonary artery stenosis, pulmonary artery occlusion and/or an increase in pulmonary flow. It is sometimes associated with right-sided heart failure and with high mortality. The prognosis of patients has recently been improved by the development of PH-specific drugs [1–3].

Atrial septal defect (ASD) is the most frequent diseases in adult congenital heart diseases. Some patients with ASD develop PH because of an extraordinary increase in pulmonary flow and/or development of pathological changes in pulmonary vascular beds. In general, the greater pulmonary flow is, the lower is PVR. In such patients, PAP decreases with closure of the ASD. On the other hand, closure of the ASD does not necessarily decrease PAP and improve clinical symptoms in patients with high PVR. At present, patients with PH and ASD who have high PVR are initially treated with PH-specific drugs [4,5]. After PVR has been substantially decreased by PH-specific drugs, surgical or transcatheter closure of the ASD can be performed. This is called the "Treat and Repair" strategy. According to the guidelines of the European Society of cardiology, closure of the ASD is allowed when PVR is less than 5 wood units [6]. When PVR is more than 5 wood units, PH-specific drugs are used at first.

There are some problems concerning the "Treat and Repair" strategy. The appropriate cut-off value of

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*Corresponding author. Phone:+81–86–235–7351; Fax:+81–86–235–7353
E-mail:akagi-s@cc.okayama-u.ac.jp (S. Akagi)

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PVR for performing closure of the ASD remains unclear. PH-specific drugs often augment pulmonary flow because of an increase in ASD shunt flow due to a decrease in PVR, and PAP does not necessarily decrease. An increase in pulmonary flow could increase shear stress of the pulmonary vasculature and might further damage the pulmonary vasculatures. We hypothesized that ASD closure followed by administration of PH-specific drugs ("Repair and Treat" strategy) would be effective for improving PH because of no extraordinary increase in shunt flow in patients with PH and ASD. Thus, this study was designed to evaluate the feasibility of the "Repair & Treat" strategy in patients with PH and ASD.

Endpoints

The primary endpoint is change in PAP and PVR from baseline to follow-up (12 weeks, 24 weeks and 48 weeks). The secondary endpoints are change in brain natriuretic peptide, tricuspid annual plane systolic excursion (TAPSE), right ventricular fractional area changes (RVFAC), tricuspid lateral annular systolic velocity waves (RVS') and inferior vena cava diameter determined by echocardiography and cardiothoracic ratio determined by chest radiography. We will examine the safety of ASD closure by assessing the patient's symptoms, hemodynamics by the right heart catheterization and urine volume.

Eligible Criteria

The study population consists of patients with PH and ASD. In patients with ASD, we check for the presence or absence of PH before closure of the ASD. We perform chest radiography, electrocardiography, blood examination, echocardiography and cardiac catheterization. ASD is defined as a secundum atrial septal detect by transthoracic and transesophageal echocardiography. PH is defined as mean PA pressure $\geq$ 25 mmHg and PA wedge pressure $\leq$ 15 mmHg by right heart catheterization. We also evaluate symptoms, use of drugs, blood pressure, heart rate, body weight, World Health Organization-functional class and 6-minute walk distance. These examinations are performed within one month after obtaining informed consent. Patients who satisfy all of the inclusion criteria are enrolled after diagnosis of PH associated with ASD (Table 1). Patients who meet any of the exclusion criteria are excluded from the study (Table 2). According to the criteria, eligible patients will give written informed consent.

Treatment

A flow chart of the study is shown in Fig. 1. Eligible patients will be undergo transcatheter closure of the ASD under general anesthesia in the catheter room. After awaking from general anesthesia, the patient will be moved to the cardiac care unit. With monitoring hemodynamics by right heart catheteriza-

Table 1 Inclusion criteria

1. Patents diagnosed with ASD
2. Patients with mean PAP $\geq$ 25 mmHg and PVR $\geq$ 5 wood units and $\leq$ 10 wood units by right heart catheterization within one month.
3. Patients with reduction of PVR after administration of 100% oxygen by right heart catheterization within one month after giving informed consent.
4. Patients with defect size of ASD $\leq$ 38 mm.
5. Patients aged 20–75 years at the time of giving consent.
6. Patients who agree to be enrolled in the study with signed written informed consent.

ASD, atrial septal defect; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

Table 2 Exclusion criteria

1. Patients with PH of other causes (collagen diseases, lung diseases, pulmonary embolism and heart failure with left ventricular dysfunction)
2. Patients with other congenital heart diseases.
3. Patients treated with PAH-specific drugs.
4. Patients with Eisenmenger syndrome.
5. Patients with bleeding or risk of bleeding.
6. Patients with atrial fibrillation.
7. Patients with pregnancy or suspected pregnancy or patients with breast-feeding.
8. Patients with moderate renal dysfunction (serum creatinine $\geq$ 1.5 mg/dl).
9. Patients with moderate liver dysfunction (serum AST or ALT $\geq$ 2-fold of standard value).
10. Patients with hypotension (systolic blood pressure $<$ 90 mmHg)
11. Patients with low cardiac output (cardiac index $<$ 2.2 l/min/m^2)
12. Patients with left ventricular dysfunction (left ventricular ejection fraction $<$ 50%).
13. Any allergy to bosentan and sildenafil.
14. Patients recognized as inappropriate by attending physician.

PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

tion, the patient will be administered bosentan (62.5 mg)(day 0). On day 1, the dose of bosentan will be increased to 125 mg/day (twice daily) and the right heart catheter will be removed. On day 3, a blood examination will be performed to check for the presence or absence of side effects to the liver and kidney. If there is no sign of side effects, sildenafil will be added (60 mg/day). On day 7, we will perform chest radiography, blood examination, electrocardiography, 6-minute walk distance test and echocardiography. If there is no sign of side effects, the patient will be discharged from the hospital. On day 28, we will again perform chest radiography, blood examination, electrocardiography, 6-minute walk distance test and echocardiography. If there is no sign of side effects, titration of bosentan will be initiated to a dose of 250 mg/day. We will perform chest radiography, blood examination, electrocardiography, 6-minute walk distance test, echocardiography and right heart catheterization at 12, 24 and 48 weeks.

Methods

PAP, right atrium pressure and pulmonary artery wedge pressure will be measured by right heart catheterization. Cardiac output is measured by Fick and thermodilution methods. PVR is calculated by mean PAP-PA wedge pressure/cardiac output. This examination will be also performed after the inhalation of 100% oxygen for 10 min. TAPSE, RVFAC, RVS' and diameter of the inferior vena cava will be measured by echocardiography.

Study Design

This study is a prospective, interventional, non-randomized, single-center study. The study was started in September 2015 at the Okayama University Hospital and will continue until December 2019. The intervention follow-up period is 12 months. This study is approved by the Ethics Committee at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (1509-006). This study has been registered at UMIN-CTR (UMIN: 000018877).

Drug Selection

We choose the bosentan and sildenafil as the PH-specific drug after the ASD occlusion. Bosentan has been widely studied and used to treat PH patients associated with congenital heart diseases. In the Bosentan Randomized Trial endothelin B receptor Antagonist Therapy-5 (BREATHE-5) showed that bosentan improved exercise capacity and hemodynam-

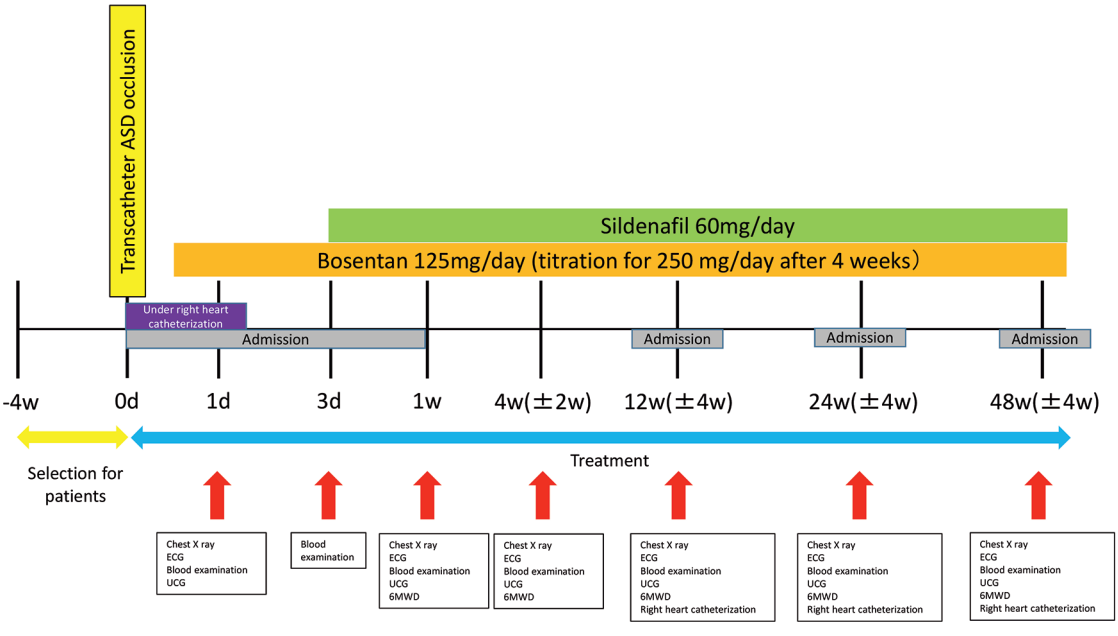

Fig. 1 Flow chart of the study. ASD, atrial septal defect; ECG, electrocardiogram; UCG, ultrasonic cardiography; 6MWD, 6-minute walk distance.

ics in patients with Eisenmenger syndrome [7]. Other study showed that long-term bosentan therapy leaded to symptomatic benefit in exercise capacity and was well tolerated in PH patients with congenital heart diseases [8]. Sildenafil has been studied to treat PH patients associated with congenital heart diseases [9]. Sildenafil is safe and well tolerated and improved exercise capacity and hemodynamics. Sequential combination therapy using bosentan and sildenafil provided the favorable short-term hemodynamic results and good survival rates [10]. We choose the combination of bosentan and sildenafil based on these studies.

Statistical Consideration

The effects of our "Repair & Treat" strategy have not been determined in patients with PH and ASD. Thus, we estimated the sample size based on the effect of each treatment option on hemodynamics changes (ASD occlusion, bosentan mono-therapy and sildenafil mono-therapy in patients with PH). Huang et al. investigated the short-term and medium-term results of transcatheter closure in patients with PH and ASD [11]. In their study, mean PAP decreased from 42 mmHg to 35 mmHg and PVR decreased from 8.5 wood units to 6.8 wood units after 12 months. Channick et al. studied the effects of bosentan on PAP and PVR in patients with PH. In their study, PVR decreased by 2.8 wood units and mean PAP decreased by 5 mmHg in patients who received bosentan [12]. Galie et al. studied the effects of sildenafil on PAP and PVR in patients with PH [13]. In their study, PVR decreased by 3.2 wood units and mean PAP decreased by 4.7 mmHg in patient who received with sildenafil. Based on the results of those studies, we hypothesized that ASD closure followed by treatment with PH-specific drugs would decrease PVR by 8 wood units compared with baseline. We calculated 8 subjects with an alpha level of 5%, a power of 80%. PAP and PVR obtained at baseline and at 12, 24, 48 weeks were compared using 1-way repeated ANOVA, followed by the post-hoc Tukey test. A p-value<0.05 was considered significant.

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