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ORIGINAL ARTICLE

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The acute effects of 30 mg vs 60 mg of intravenous Fasudil on patients with congenital heart defects and severe pulmonary arterial hypertension

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Abstract

Objective: The optimal dose of Fasudil is still controversial in congenital heart disease accompanied with severe pulmonary hypertension (CHD-PAH). This study aimed to compare acute hemodynamic changes after different doses of Fasudil in 60 consecutive adult patients with CHD-PAH.

Design: Prospective randomized controlled trial.

Setting: Tertiary cardiology center.

Patients: Adult patients with CHD-PAH.

Interventions: Patients were randomized to Fasudil 30 or 60 mg.

Outcome Measures: The hemodynamic parameters were measured at baseline and after 30 minutes of Fasudil through right cardiac catheterization. Blood gas results were obtained from the pulmonary artery, right ventricle, right atrium, superior and inferior vena cava, and femoral artery. Pulmonary vascular resistance (PVR) and systemic arterial resistance (SVR) were calculated.

Results: The changes in systolic pulmonary artery pressure (sPAP) (−13.1% vs −9.3%, $P < .05$), diastolic PAP (dPAP) (−17.6% vs −14.5%, $P < .05$), mean PAP (mPAP) (−12.4% vs −8.5%, $P < .05$), and PVR (−35.8% vs −22.2%, $P < .05$) were more pronounced in the 60-mg group than in the 30-mg group. All patients had no obvious adverse reactions related to peripheral blood pressure.

Conclusions: Fasudil could improve the hemodynamics of patients with CHD-PAH, especially with the 60-mg dose. There were no serious adverse reactions.

KEYWORDS

congenital heart defects, pulmonary arterial hypertension, Rho kinase inhibitor

1 | INTRODUCTION

About 15%-20% of patients with congenital heart disease also present varying degrees of pulmonary hypertension, which is the most common complication of congenital heart diseases and one of the most important causes of disability and death.[1,2] If early intervention is not undertaken, these patients can eventually develop the Eisenmenger syndrome.[3] An epidemiological study showed that about 30% of untreated congenital heart diseases were accompanied with pulmonary artery hypertension, and that about 15% still had pulmonary artery hypertension after surgical treatment.[4]

The current approach for patients with pulmonary arterial hypertension due to congenital heart disease is the use of vasodilators, including prostanoids,[5,6] endothelin receptor antagonists,[7,8] and phosphodiesterase-5 inhibitor.[9] These drugs have some efficacy, but they are used to treat the consequence of pulmonary hypertension rather than its cause. In recent years, a large body of evidence revealed that Rho kinase is involved in the development of pulmonary

hypertension.[10,11] Animal experiments and clinical studies showed high Rho kinase activity in rat models of pulmonary hypertension[12] and tissues from lung and pulmonary arteries of patients with severe pulmonary hypertension.[13]

Fasudil is currently the only available intravenous Rho kinase inhibitor in China. Unlike calcium antagonists, Fasudil competes with adenosine triphosphate (ATP) for the ATP binding site in the catalytic region of Rho kinase to block Rho kinase activity and inhibit myosin light chain (MLC) phosphorylation at the final stage of vascular smooth muscle contraction, thus relaxing the spasmodic and contracted vascular smooth muscle and acting as a vasodilator. The therapeutic effect of Fasudil on pulmonary hypertension was reported in 2006 in Japan[14] and by subsequent studies.[15-18] Xiao et al also reported the therapeutic effect of Fasudil on congenital heart disease accompanied with severe pulmonary hypertension.[19] Nevertheless, the optimal dose of Fasudil is still controversial.

We hypothesized that Fasudil can improve the hemodynamics of patients with congenital heart disease and severe pulmonary hypertension. Therefore, the aim of the present study was to compare the acute changes in hemodynamics after the rapid intravenous infusion of different doses of Fasudil in adult patients with congenital heart disease and severe pulmonary hypertension.

2 | METHODS

2.1 | Study design and patients

This was a prospective randomized controlled trial of adult patients with congenital heart disease and pulmonary arterial hypertension who visited the Department of Cardiology of Xuzhou Central Hospital between June 2013 and June 2016. The trial was approved by the ethics committee of Xuzhou Central Hospital. All patients signed an informed consent form. The study was carried out in accordance with the Declaration of Helsinki.

The inclusion criteria were: (1) adult (18-60 years of age) patients with congenital heart disease and severe pulmonary hypertension diagnosed by color Doppler echocardiography; (2) planned to undergo right heart catheterization; (3) no history of drugs or treatments targeting pulmonary blood vessels such as calcium ion antagonists; and (4) severe pulmonary hypertension according to the grading criteria of the World Health Organization (WHO) for pulmonary hypertension[20]: elevation of mean pulmonary artery pressure at rest (mPAP) ≥45 mm Hg and pulmonary capillary wedge pressure (PCWP) < 15 mm Hg. Contraindications for right heart catheterization were: (1) shock; (2) severe metabolic disease; (3) severe peripheral vascular disease; (4) severe liver or kidney dysfunction; (5) active infection; (6) moderate and severe anemia; or (7) any other diseases that could increase the risks associated with interventional catheterization.

2.2 | Grouping

After being diagnosed with severe pulmonary hypertension by right heart catheterization, all eligible and consenting patients were randomized to the 30-mg Fasudil group and 60-mg Fasudil group using sequential sealed envelopes. The envelopes were prepared by an independent statistician using a random number table. An envelope was opened by the physician after the informed consent form was signed.

2.3 | Blinding

The patients and the assessors were blinded to the grouping. Only the physician giving the drug was aware of the grouping.

2.4 | Baseline data

Baseline data (gender, age, height, weight, blood gas, and blood cells) were collected after admission. All patients underwent brain natriuretic peptide (BNP) measurement and color Doppler echocardiography to determine the type of congenital heart defect (atrial septal defect, ventricular septal defect, and patent ductus arteriosus) and to assess the function of the heart.

2.5 | Hemodynamic measurements

The patients were placed in the supine position (without oxygen). The right femoral artery was selected as the puncture point. A 6F sheath was inserted under local anesthesia with 3-5 mL of 5% lidocaine and a Swan-Ganz floating catheter (Edwards Lifesciences Co., Ltd., Irvine, California) was placed through the sheath for right heart catheterization. The height of the axillary frontline at atmospheric pressure was set as zero and a MP60 multifunction recorder (Philips, Best, the Netherlands) was connected. Mean right arterial pressure (RAP), systolic pulmonary arterial pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP), heart index (CI), pulmonary blood flow (Qp), and mean systemic arterial pressure (mSAP) were recorded. Blood gas results were obtained from the pulmonary artery, right ventricle, right atrium, superior and inferior vena cava, and femoral artery. Pulmonary vascular resistance (PVR) and systemic arterial resistance (SVR) were calculated.[21]

2.6 | Fasudil treatment

Fasudil was given after measuring the baseline hemodynamics. In the 30-mg and 60-mg groups, 30 or 60 mg of Fasudil (Tianjin Chase Sun Pharmaceutical Co., Ltd., Tianjin, China; approval number: H20020356) in 50 ml of saline was intravenously infused over 30 minutes. The hemodynamic parameters described above were recorded again after the end of infusion (at 30 minutes). The changes in the hemodynamic parameters were assessed immediately after the end of infusion. Because the plasma half-life is 16 minutes, the plasma concentration will peak at the end of infusion and will then rapidly decrease. The adverse reactions (decreased systemic blood pressure, dizziness, palpitation, rash, dyspnea, digestive tract

symptoms, intracranial bleeding, gastrointestinal bleeding, blushing, abdominal distension, nausea, and headache) were observed over 120 minutes after the intravenous injection.

2.7 | Statistical analysis

Data were processed using SPSS 14.0 for Windows (SPSS Inc, Chicago, Illinois). Continuous data were found to be normally distributed according to the Kolmogorov-Smirnov test. Continuous data were presented as mean ± standard deviation and analyzed using the paired *t* test (comparisons for before/after treatment) or the independent sample *t* test (between groups). Two-sided *P* values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the patients

In this study, 63 patients were recruited, but 3 had low blood pressure during catheterization (SBP < 90 mm Hg) and were excluded. The baseline data of the 60 included patients are shown in Table 1. There were no differences in gender, age, height, weight, blood oxygen saturation, hemoglobin, types of congenital heart disease, and BNP and between the 30-mg and 60-mg Fasudil groups (all *P* > .05). None of the patients had received interventional closure or surgical repair.

TABLE 1 Baseline data

	30-mg group (*n* = 30)	60-mg group (*n* = 30)	*P* value
Age (years)	36.6 ± 13.7	38.9 ± 17.2	.791
Gender (male)	11 (36.7%)	13 (43.3%)	.682
Height (cm)	170.6 ± 12.1	168.5 ± 11.8	.843
Weight (kg)	61.5 ± 10.5	59.6 ± 11.8	.713
Blood oxygen saturation (%)	90.1 ± 7.6	91.3 ± 7.9	.941
Hemoglobin (g/L)	134.6 ± 13.6	137.8 ± 15.7	.690
Congenital heart disease (cases)			
ASD	7 (23.3%)	8 (26.7%)	.723
VSD	5 (16.7%)	6 (20.0%)	.674
PDA	11 (36.7%)	9 (30.0%)	.591
Complex[a]	6 (20.0%)	5 (16.7%)	.692
BNP (ng/mL)	876.4 ± 64.7	913.2 ± 73.8	.893
WHO-FC			
II	7 (23.3%)	5 (16.7%)	.581
III	18 (60.0%)	22 (73.3%)	.473
IV	5 (16.7%)	3 (10.0%)	.422

Abbreviations: ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect; WHO-FC, WHO function class.
[a]Complex congenital heart diseases refer to hearts presenting abnormalities in at least two cardiovascular structures.

3.2 | Hemodynamics

There were no differences in hemodynamics between the two groups before the Fasudil infusion (all *P* > .05) (Table 2). In both groups, sPAP, dPAP, mPAP, and PVR were all significantly decreased and CI was increased after the intravenous infusion of Fasudil compared with baseline (all *P* < .05). PCWP was normal in both groups, indicating that the patients did not have left heart-related pulmonary hypertension, and there was no significant change after infusion.

When comparing the changes in hemodynamics between the two groups, it was observed that the changes in sPAP, dPAP, mPAP, and PVR were more pronounced in the 60-mg group than in the 30-mg group (sPAP: −13.1% vs −9.3%, *P* < .05; dPAP: −17.6% vs −14.5%, *P* < .05; mPAP: −12.4% vs −8.5%, *P* < .05; and PVR: −35.8% vs −22.2%, *P* < .05). Importantly, the reduction in PVR was more important in the 60-mg group compared with the 30-mg group. There was no significant change in Qp in the two groups.

3.3 | Adverse reactions

All patients had no obvious adverse reactions related to peripheral blood pressure after the intravenous injection of Fasudil, but peripheral blood pressure was decreased slightly, with a maximum decrease of ≤15% in SVR (Table 2). Two patients in the 30-mg group had transient dizziness and nausea. One patient in the 60-mg group had abdominal pain, but the pain disappeared without special treatment. No acute pulmonary edema occurred.

4 | DISCUSSION

Fasudil can be used to treat pulmonary arterial hypertension due to congenital heart disease, but the optimal dose is still controversial. Therefore, the present study aimed to compare the acute changes in hemodynamics after the rapid intravenous infusion of different doses of Fasudil in adult patients with congenital heart disease combined with pulmonary arterial hypertension. The results showed that Fasudil could improve the hemodynamics of patients with congenital heart disease combined with pulmonary arterial hypertension, especially with the 60-mg dose. There were no serious adverse reactions.

Congenital heart diseases represent the main cause of pulmonary hypertension.[1,2,22] The main pathogenic factors are high blood flow shear stress, anoxia, and inflammation.[1,2] When there are different congenital defects or abnormal shunts, the systemic circulation volume flows through the defect or abnormal shunt to the pulmonary circulation, increasing the pulmonary blood flow and elevating the pulmonary artery pressure, resulting in damage to the endothelial cells. Damaged endothelial cells lose barrier function, induce immune and inflammatory reactions, and increase the formation of microthrombi, further leading to the obstruction of pulmonary arterioles thereby increasing the pulmonary artery pressure.[23] At the same time, the endothelial dysfunction causes imbalances of vasoconstriction and vasodilation factors, resulting in pulmonary

TABLE 2 Comparison of the changes in hemodynamics between the two groups before and after intravenous Fasudil

	30-mg group			60-mg group			
	Before	After	After/before difference	Before	After	After/before difference	*P*
mSAP (mm Hg)	85.1 ± 12.3	83.7 ± 11.8	−2.1 ± 0.2	83.9 ± 11.9	81.9 ± 11.6	−1.9 ± 0.3	.455
mRAP (mm Hg)	6.8 ± 2.1	5.6 ± 1.8	−1.5 ± 0.3	6.4 ± 2.0	5.0 ± 1.6	−1.4 ± 0.4	.738
sPAP (mm Hg)	109.3 ± 16.6	99.1 ± 15.3**	−12.5 ± 3.1	107.9 ± 15.8	93.8 ± 14.7****	−17.3 ± 5.9	<.001
dPAP (mm Hg)	35.9 ± 5.7	30.7 ± 6.4**	−5.2 ± 1.3	34.6 ± 6.2	28.5 ± 5.9****	−8.1 ± 2.2	.027
mPAP (mm Hg)	63.7 ± 8.6	58.3 ± 8.5**	−4.2 ± 1.0	62.9 ± 8.8	55.1 ± 7.8****	−8.2 ± 1.8	.018
PVR (Wood)	9.9 ± 4.3	7.7 ± 3.9**	−2.1 ± 0.8	9.5 ± 4.9	6.1 ± 4.8****	−3.7 ± 1.1	.032
SVR (Wood)	19.2 ± 5.7	18.1 ± 5.2	−1.2 ± 0.3	19.0 ± 6.1	17.9 ± 5.5	−1.3 ± 0.3	.981
PCWP (mm Hg)	8.5 ± 3.0	8.6 ± 3.5	0.4 ± 0.1	8.4 ± 4.0	8.5 ± 3.9	0.2 ± 0.07	.956
Qp (L/min/m^2)	5.1 ± 1.4	5.4 ± 1.6	0.3 ± 1.4	5.0 ± 1.5	5.7 ± 1.6	0.7 ± 1.6	.471
CI (L/min/m^2)	2.9 ± 0.9	3.1 ± 1.1*	0.3 ± 0.1	3.0 ± 0.8	3.5 ± 1.6***	0.4 ± 0.1	.897
SaO_2 (%)	90.1 ± 7.6	91.3 ± 7.9	1.1 ± 0.4	91.2 ± 8.1	93.0 ± 8.6	1.5 ± 0.3	.945

*P < .05 vs before treatment in the 30-mg group.
**P < .01 vs before treatment in the 30-mg group.
***P < .05 vs before treatment in the 60-mg group.
****P < .01 vs before treatment in the 60-mg group.

vascular remodeling, pulmonary vascular bed reduction, and progressive elevation of total pulmonary artery resistance.[24]

Rho-associated kinase has been identified as playing a key role in the formation of pulmonary hypertension.[10,11] Rho is present in the smooth muscle cells of brain, heart, lung, and peripheral arteries. Ras regulates many biological behaviors and functions of cells, such as contraction, adhesion, migration, proliferation, apoptosis, and gene expression by activating downstream targets.[25] The RhoA/Rho kinase signaling pathway is involved in the formation of pulmonary hypertension.[26,27] Even in the presence of persisting vasoconstriction factors, the use of Rho kinase inhibitor in pulmonary artery hypertension will achieve satisfactory therapeutic effects.[10,11,16-18,28] Nevertheless, the dose of Fasudil for the treatment of patients with pulmonary hypertension is still unknown. There are few clinical reports on its use in patients with congenital heart disease and pulmonary hypertension.

In the present study, Fasudil, which is the only intravenous Rho kinase inhibitor available in China, was used to treat patients with congenital heart disease and severe pulmonary hypertension, and the 60-mg dose was compared with the standard 30-mg dose. The results showed that the two doses of Fasudil could reduce pulmonary arterial pressure and total pulmonary arterial resistance, but did not reduce peripheral vascular pressure. In addition, the cardiac index was significantly increased, without changing the PCWP, which reflects the left ventricular end-diastolic pressure. These effects are well-known effects of Fasudil in pulmonary hypertension in patients without congenital heart diseases.[14,16-18,28] These results in patients without congenital heart diseases make sense because the pulmonary artery hypertension limits cardiac output. On the other hand, Fasudil may have other effects in patients with shunting lesions.[19] The cardiac index may decrease slightly because using pulmonary vasodilators in these patients may result in increased left-to-right shunting with increasing pulmonary flow. If pulmonary flow rises significantly, CI may fall slightly. Alternatively, the cardiac index may remain relatively stable because the feedback loops for cardiac output are not changed by pulmonary vasodilation. Interestingly, the pulmonary blood flow was not significantly changed in the present study and the exact mechanisms of Fasudil in this patient population remain to be understood. In untreated patients with congenital heart disease combined with pulmonary arterial hypertension, the Eisenmenger syndrome is not characterized by low cardiac output, but rather progressive cyanosis because of right-to-left shunting. Therefore, the increase in the cardiac index might not be clinically significant. Nevertheless, the present study showed that the high dose (60 mg) could more significantly reduce the parameters of pulmonary circulation pressure than the routine dose (30 mg), while the peripheral blood pressure was not further reduced and there was no increase in the frequency of adverse effects. Therefore, these results support that intravenous Fasudil infusion improves the acute hemodynamics of congenital heart disease with severe pulmonary hypertension and that the high dose was more effective than the low dose in treating congenital heart disease with severe pulmonary hypertension.

The present study is not without limitations. It was a single center study with a limited number of patients. In addition, we could not perform subgroup analyses according to the type of congenital heart disease. There was no evaluation of the long-term effects. Additional studies with more patients and from multiple centers are necessary to confirm those results.

In conclusion, Fasudil could improve the hemodynamics of patients with congenital heart disease combined with pulmonary arterial hypertension, especially with the 60-mg dose. There were no serious adverse reactions.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Hongyun Ruan carried out the studies, participated in data collection, and drafted the manuscript. Yigang Zhang and Ru Liu performed the statistical analysis and participated in its design. Xiangjun Yang helped to draft the manuscript. All authors read and approved the final manuscript.

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