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ORIGINAL ARTICLE

Intravenous fasudil improves in-hospital mortality of patients with right heart failure in severe pulmonary hypertension

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The in-hospital mortality of severe pulmonary hypertension (PH) with right heart failure (RHF) is high despite the use of vasoactive and PH-specific therapies. We conducted a prospective analysis evaluating the safety and outcomes of fasudil hydrochloride (Chuan Wei) therapy in acute RHF. PH patients hospitalized between April 2009 and November 2010 were treated with 30 mg of i.v. fasudil three times daily over 30 min, until they experienced relief of RHF symptoms. Adverse and serious adverse events were recorded. Odds ratios (ORs) and 95% confidence intervals were calculated for both in-hospital mortality and re-hospitalization. Multivariate adjustments were made for age, gender and World Health Organization functional class. There were no significant differences between the fasudil group and the control group in demographics, hemodynamics, and PH-specific and vasoactive therapies. Of the 209 study patients, 3 of the 74 patients (4.1%) in the fasudil arm died, and 19 of the 135 patients (14.1%) in the control arm died ($P = 0.005$). Fasudil decreased both in-hospital mortality (OR = 0.258 (0.074–0.903); $P = 0.034$) and 30-day re-hospitalization (OR = 0.200 (0.059–0.681); $P = 0.010$). Fasudil was well tolerated; one patient discontinued treatment. Intravenous fasudil may be given safely in patients with PH and acute RHF, and may reduce the rates of both in-hospital mortality and 30-day re-hospitalization.
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INTRODUCTION

Pulmonary arterial hypertension (PAH), a progressive and fatal disease caused by a variety of disorders, is characterized by an increase in pulmonary vascular resistance (PVR), abnormal sustained pulmonary vasoconstriction and progressive structural remodeling of the pulmonary arteries, ultimately leading to right ventricular failure and death.[1–3] Pulmonary hypertension (PH) is an incurable disease characterized by sustained vasoconstriction, progressive vascular remodeling and irreversible right heart dysfunction. The in-hospital mortality of severe PH with acute right heart failure (RHF) is high despite the use of vasoactive and PH-specific therapies, including i.v. dopamine, dobutamine, milrinone, i.v. or inhaled prostacyclin analogs, and/or oral endothelin receptor antagonists and phosphodiesterase-5 inhibitors,[4,5] as well as other promising new drugs.[6,7] During hospitalizations for other comorbid diseases, such as pneumonia, patients' World Health Organization functional class (WHO-FC) may deteriorate into WHO-FC III or WHO-FC IV, and often the event is fatal.[8–10] There is a need to develop an effective therapy to improve these patients' short-term outcomes.

Fasudil hydrochloride (Chuan Wei), a small G-protein RhoA inhibitor, exerts acute pulmonary vasodilator effects in patients with severe PAH.[11] Rho-kinase is activated in animal models of PAH associated with enhanced pulmonary vasoconstriction, proliferation, impaired endothelial vasodilator function and pulmonary vascular remodeling.[11–17] A variety of preclinical and clinical studies have suggested that the Rho-kinase pathway is involved in vascular signaling in cardiovascular disease[18,19] and PH.[20–26] Recently, a pilot double-blinded, placebo-controlled study demonstrated that pulmonary hemodynamics exhibited improvement following oral treatment with an extended-release formulation of fasudil hydrochloride.[27] The Rho-kinase inhibitor fasudil is currently approved in Japan and China as a treatment to prevent cerebral vasospasm in aneurysmal subarachnoid hemorrhage.

Rho-kinase inhibitors are a promising new class of drugs for RHF in severe PH. Intravenous fasudil, a Rho-kinase inhibitor, is a promising

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agent for PH therapy.[12,22,25,28] In this paper, we report the efficacy of i.v. fasudil in hospitalized patients with severe PH and RHF.

METHODS

The protocol for this prospective, open label study was approved by the Institutional Ethics Committee of Shanghai Pulmonary Hospital (approval number: K10-058) and conformed to the principles outlined in the Declaration of Helsinki. All participants who received fasudil treatment provided informed consent (children's guardians signed the consent form).

Inclusion/exclusion criteria

Patients were recruited from Shanghai Pulmonary Hospital, the largest referral center in China, which has a large number of patients diagnosed with idiopathic PAH.[29] All patients were admitted and PH was diagnosed according to the Nice Classification.[30] The PH patients either were receiving specific vasodilators prior to their hospitalization or were started on them during their incident hospitalization. All patients met the following criteria for the diagnosis of PH: (i) a mean pulmonary arterial pressure (mPAP) $\geqslant 25$ mm Hg at rest as determined via right heart catheterization (RHC) or a pulmonary artery systolic pressure >50 mm Hg[31] as determined via transthoracic echocardiography for patients who were too ill or unwilling to undergo RHC; (ii) classification as WHO-FC III or IV; and (iii) receiving vasoactive agents for RHF, with or without PAH-specific drugs (such as endothelin receptor antagonists, prostacyclin-analogues or phosphodiesterase-5 inhibitors).

Patients were excluded for the following reasons: classification as WHO-FC I or II; not combining the vasoactive medications (for example, dopamine or dobutamine); not admitted to the hospital and not assessed via an RHC or transthoracic echocardiography.

Study design

The investigators began using fasudil hydrochloride (*Brand*: Chuan Wei, Tianjin Chase Sun Pharmaceutical, No. 20, Quanfa Road, Tianjin Wuqing Development Area, China) in April 2009. Although the drug had not been approved for PH in China, it had been used off-label to treat patients with severe PH and acute RHF who exhibited either no response or a poor response to standard clinical therapies for cardiogenic shock. Acute RHF was defined as either new-onset or rapidly worsening heart failure requiring urgent inpatient therapy. A patient exhibiting evidence of volume overload or low cardiac output (CO) syndrome requiring i.v. diuretic therapy or vasopressor therapy was considered to have acute RHF.[10]

Between April 2009 and November 2010, 209 patients with PH were consecutively enrolled into this prospective cohort study. Eligible patients were randomly assigned to either an experimental group (fasudil group) or a control group (no-fasudil group) according to a pre-specified computer-generated scheme (2:1 ratio).The protocol was open label and not blinded.

Diuretics were used in all patients. Dobutamine and dopamine infusions, the preferred inotropic agents, were usually administered at initial doses of 2.0 μg kg^{-1} per minute and titrated up to doses of 3–10 μg kg^{-1} per minute in the presence of signs of persistently low CO (for example, low hypotension, altered mentation or oliguria). Milrinone was used at the usual maintenance dose of 0.25–0.75 μg kg^{-1} per minute. All patients received inotropic infusion and/or PAH-specific drugs (endothelin receptor antagonists, prostacyclin-analogues or phosphodiesterase-5 inhibitors) until relief of severe RHF was achieved (for example, improvement of volume overload or low CO syndrome) and the patient either was discharged or died.

In the experimental group, fasudil infusions were initiated as an add-on to pre-existing therapy with vasoactive drugs and/or PAH-specific drugs; 30 mg of fasudil was intravenously injected over 30 min three times daily until relief of acute RHF was achieved. Doses were reduced by half for children.

Outcome measures

Assessment of clinical outcomes was based on in-hospital mortality and 30-day re-hospitalization for cardiovascular symptoms. We did not observe more than one re-hospitalization for any patient enrolled in our study. Data were obtained during follow-up or via telephone interview. Any adverse events that occurred during administration of fasudil were recorded. Routine blood, liver and renal function parameters were assessed before and after the study.

Hemodynamic studies

RHC was performed in some of the patients ($n=58/121$) during hospitalization. Baseline hemodynamic variables, including mPAP, mean right atrial pressure (mRAP) and pulmonary capillary wedge pressur, were measured. CO was measured in triplicate using a thermodilution technique with ice-cold isotonic sodium chloride solution, except in unrepaired congenital heart disease, in which CO was measured using the indirect Fick method. Cardiac index was calculated by dividing CO by body surface area. PVR) was calculated by dividing the difference between mPAP and pulmonary capillary wedge pressure by CO.

Statistical analysis

Baseline characteristics are reported either as the mean ± s.d. or as medians and quartiles for continuous variables, and as percentages for categorical variables. The Kolmogorov–Smirnov test was applied to assess data distribution. Baseline characteristics of study participants were compared between groups using the independent samples *t*-test, and the Mann-Whitney U-test was used to assess data that were not normally distributed. The chi-square test was used for dichotomous variables. The predefined endpoints were in-hospital mortality and re-hospitalization. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for in-hospital mortality and re-hospitalization.

Binary logistic regression was used to assess bivariate relationships. A two-tailed *P* value less than 0.05 indicated a statistically significant difference.

Univariate regression analyses for in-hospital mortality and 30-day re-hospitalization were performed first. Risk factors at the 0.05 level were significant. The pre-specified risk factors were sex, age, WHO-FC, tricuspid annular plane systolic excursion, laboratory test results such as for N-terminal pro-B type natriuretic peptide, systolic blood pressure, diastolic blood pressure, heart rate, hemodynamic variables (CO, mRAP, mPAP, PVR and pulmonary capillary wedge pressure), PAH-specific drugs (i.v./inhaled prostacyclin analogs, and/or oral endothelin receptor antagonists or phosphodiesterase-5 inhibitors) or vasoactive agents (i.v. dopamine, dobutamine and milrinone). Each continuous value was transformed into a binary variable, using either its mean or median as a cutoff.

Multivariate logistic regression analysis was performed to determine the relationship between in-hospital mortality and fasudil administration, adjusted for WHO-FC. Using multivariate logistic regression, the relationship between 30-day re-hospitalization and fasudil was analyzed, adjusting for dobutamine. We reported ORs with 95% CIs. The analyses were performed using specific statistical software (SPSS software, version 15.0, Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 209 consecutive patients with RHF-related symptoms met the inclusion criteria and were prospectively entered into this study. The study population included patients with idiopathic PAH (37.8%), PAH associated with congenital heart disease (17.2%), PAH associated with connective-tissue disease (13.9%), chronic thromboembolic PH (15.3%), PH with lung disease (9.0%) and other forms of PH (7.7%) (Table 1). A total of 74 patients treated with fasudil and 135 control subjects were studied. Among the 74 patients treated with fasudil (27 male and 47 female), the median age was 42.0 (29.5–58.3) years and the mean body mass index was 21.35 (14.35–30.08) kg m^{-2}. The 135 control subjects (50 male and 85 female) had a median age of 21.35 (14.35–30.08) years and a median body mass index of 21.35 (14.35–30.08) kgm^{-2}. Of the patients in the experimental group, 22 (29.7%) were classified as WHO-FC IV and 52 (70.3%) as WHO-FC III. Of the patients in the control group, 29 (21.5%) were classified as WHO-FC IV and 106 (78.5%) as WHO-FC III. The demographic and clinical characteristics of the two groups at the beginning of study are shown in Table 1.

Table 1 Baseline characteristics of fasudil group and no-fasudil group

	Fasudil (n = *74*)	*No-fasudil* (n = *135*)	P *value*
Age (years)	42.0 (29.5–58.3)	37.0 (26.0–54.0)	0.140
Gender, female (%)	47 (63.5)	85 (63.0)	0.937
BMI (kg m^{-2})	21.35 (14.35–30.08)	20.73 (12.62–20.73)	0.672
SBP (mm Hg)	107.1 ± 16.0	111.6 ± 17.9	0.692
DBP (mm Hg)	72.6 ± 12.6	74.1 ± 13.4	0.616
HR (b.p.m.)	92.7 ± 15.7	91.0 ± 15.7	0.606
Classifications, n *(%)*			0.230
IPAH	26 (35.1)	53 (39.3)	
APAH with CHD	8 (10.8)	28 (20.7)	
ES	5	10	
Shunt repaired	3	18	
APAH with CTD	15 (17.6)	14 (10.4)	
SLE	11	8	
PM	1	—	
MCTD	0	1	
SSc	3	5	
CTEPH	16 (21.6)	16 (11.9)	
PH with lung diseases	6 (8.1)	13 (9.6)	
COPD	4	8	
Bronchiectasis	1	3	
Pneumonoconiosis	1	—	
ILD	—	1	
Chest deformity	—	1	
APAH with left heart	2 (2.7)	5 (3.7)	
Others			
Pulmonary vasculitis	3 (4.1)	6 (4.4)	
WHO-FC IV (%)	22 (29.7)	29 (21.5)	0.184
Lab examinations			
CR (μmol l^{-1})	60.5 (49.0–73.8)	66.1 ± 21.9	0.286
ALT (U l^{-1})	19.0 (14.0–30.0)	22.0 (14.0–33.5)	0.163
NT-proBNP (ng l^{-1})	1314 (678, 2278.3)	1120 (700, 2145)	0.652
DE (n = *63/108)*			
PASP (mm Hg)	99.0 ± 26.0	97.8 ± 27.7	0.560
TAPSE (cm)	1.61 ± 0.4	1.64 ± 0.3	0.619
RHC (n = *58/121)*			
mRAP(mm Hg)	9.0 (–1.0 – 29.0)	9.0 (–1.0 – 26.0)	0.838
mPAP (mm Hg)	59.0 (45.3–70.0)	63.0 (49–77)	0.232
PCWP (mm Hg)	10 (7–12)	9 (8–12)	0.617
PVR (wood unit)	14.0 (9.12–20.7)	15.5 (10.59–22.81)	0.378
CO (l min^{-1})	3.37 (2.67–4.53)	3.33 (2.51–4.40)	0.711
Specific drug therapy			
PDEI, *n* (%)	50 (67.6)	81 (60.0)	0.279
Prostanoid, *n* (%)	32 (43.2)	53 (39.3)	0.575
ERA, *n* (%)	9 (12.2)	15 (11.1)	0.820
Vasoactive drug therapy			
Dopamine, *n* (%)	68 (91.9)	122 (90.4)	0.714
Dobutamine, *n* (%)	27 (36.4)	21 (20.4)	0.114
Milrinone, *n* (%)	7 (9.5)	10 (7.4)	0.604

Abbreviations: ALT, alanine transaminase; APAH, associated pulmonary arterial hypertension; BMI, body mass index; CHD, congenital heart disease; CI, confidence interval; CO, cardiac output; CR, creatinine; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; COPD, chronic obstructive pulmonary diseases; DBP, diastolic blood pressure; DE, Doppler echocardiography; ERA, endothelin receptor antagonist; ES, Eisenmengersyndrome; HR, heart rate; ILD, interstitial lung disease; IPAH, idiopathic pulmonary artery hypertension; MCTD, mixed connective tissue disease; mPAP, mean pulmonary artery hypertension; mRAP, mean right atrium pressure; NT-proBNP, N-terminal pro-Btype natriuretic peptide; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PDEI, Phosphodiesterase type-5 inhibitors; PM, polymyositis; PVR, periphery vessel resistance; RHC, right heart catheterization; SBP, systolic blood pressure; SLE , systemic lupus erythematous; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.
Values are expressed as *n* (%) or mean ± s.d. or median (25th, 75th percentiles).

There were no significant differences between the experimental group and the control group regarding age, sex, body mass index, classifications, WHO-FC, systolic blood pressure, diastolic blood pressure, heart rate, laboratory test results, tricuspid annular plane systolic excursion and pulmonary artery systolic pressure by echocardiogram, or hemodynamic parameters as determined via catheterization (mRAP, mPAP, pulmonary capillary wedge pressure, PVR and CO) (Table 1).

At baseline, there were no differences between the two groups regarding the use of either PAH-specific drugs or vasoactive agents (Table 1).

Outcomes

Thirty-three patients received >1 week therapy; the longest duration of fasudil therapy was 28 days. The median duration of fasudil treatment was 8 days (5, 13.5). There were 19 deaths (8 males and 11 females; 8 were children and 1 was an elderly patient ⩾60 years of age) in the control group *vs.* 3 deaths in the fasudil group (all female patients).

Logistic regression model

The in-hospital mortality in both groups was 10.5%. The in-hospital mortality was 4.1% in the fasudil group compared with 14.1% in the control group ($P=0.005$). The unadjusted OR for both in-hospital mortality and 30-day re-hospitalization owing to RHF was 0.258 (95% CI: 0.074–0.903; $P=0.034$) and 0.200 (95% CI: 0.059–0.681; $P=0.010$). The predictors of in-hospital mortality and 30-day re-hospitalization are shown in Table 2. WHO-FC was associated with an increased risk of in-hospital mortality. Dobutamine administration was associated with an increased risk of 30-day re-hospitalization. Using multivariate logistic regression to adjust for WHO-FC, in-hospital mortality was associated with fasudil administration (adjusted OR, 0.141; 95% CI, 0.036–0.549; $P=0.005$). The multivariate logistic regression analysis of dobutamine and fasudil administration demonstrated that only fasudil was associated with 30-day re-hospitalization (adjusted OR, 0.214; 95% CI, 0.063–0.733; $P=0.014$) (Table 3).

Adverse events

One patient discontinued therapy because of an allergic rash. Of the patients treated with fasudil, none had abnormalities in hepatic or renal function during follow-up. The routine blood, liver and renal function parameters were not significantly different following treatment compared with before treatment ($P>0.05$) (Table 4).

DISCUSSION

In this study, we evaluated the efficacy of i.v. fasudil in hospitalized patients with severe PH and RHF. Our study is the first to identify fasudil as a potential therapy for this syndrome. Fasudil improved both in-hospital mortality and 30-day re-hospitalization and was well tolerated.

Acute RHF in patients with PH is often fatal. In a recent study by Sztrymf and colleagues,[9] patients with PAH who were hospitalized for acute heart failure in the intensive care unit had a mortality rate of 42%.[10] In our study, the overall in-hospital mortality for both groups was 10.5%, lower than that reported by Sztrymf *et al.*[9,10] In the study by Sztrymf and colleagues, all patients had severe heart failure and required hospitalization in an intensive care unit to manage low CO and its sequelae. However, our study included more PH patients classified as WHO-FC III during hospitalization.

Why did fasudil hydrochloride infusion reduce in-hospital mortality and 30-day re-hospitalization in our study? We believe that fasudil hydrochloride infusion improves hemodynamic parameters.[22,24,25,27] Fukomoto *et al.*,[25] in 2005, reported a statistically significant 17% reduction in PVR without a change in systemic blood pressure, although there was no significant change in either mPAP or CI. In

Table 2 Univariate analysis for 30-day re-hospitalization and in-hospital mortality

	30-day re-hospitalization		*In-hospital mortality*	
	OR (95%CI)	P *value*	*OR (95%CI)*	P *value*
Age (years)< 38 *vs.*⩾38	0.976 (0.490–1.946)	0.946	0.642 (0.262–1.575)	0.333
Gender	0.574 (0.286–1.150)	0.117	0.961 (0.386–2.389)	0.961
WHO-FC	1.647 (0.775–3.501)	0.194	15.300 (5.279–44.344)	<0.001
SBP (mm Hg)	0.977 (0.949–1.006)	0.126	1.004 (0.901–1.118)	0.946
DBP (mm Hg)	0.960 (0.903–1.021)	0.196	1.006 (0.871–1.162)	0.938
HR (b.p.m.)	1.003 (0.976–1.031)	0.821	0.995 (0.871–1.137)	0.941
Group (fasudil/no fasudil)	0.200 (0.059–0.681)	0.010	0.258 (0.074–0.903)	0.034
mRAP (mm Hg), <9.0 *vs.* ⩾9.0	1.185 (0.530–2.650)	0.679	1.015 (0.336–3.066)	0.979
mPAP (mm Hg), <62.9 *vs.* ⩾62.9	0.895 (0.486–1.649)	0.722	3.51 (0.993–14.160)	0.051
PVR (wood units), <15.0 *vs.* ⩾15.0	1.125 (0.544–2.367)	0.754	1.639 (0.515–5.214)	0.403
CO (l/min), <3.33 *vs.* ⩾3.33	0.778 (0.264–1.661)	0.516	0.673 (0.205–2.205)	0.513
CR (μmol l^{-1})	0.870 (0.621–1.218)	0.418	1.002 (0.997–1.006)	0.442
ALT (U l^{-1})	0.947 (0.861–1.056)	0.365	0.989 (0.967–1.012)	0.354
NT-proBNP (ng l^{-1})	1.001 (0.999–1.001)	0.749	0.999 (0.998–1.001)	0.306
TAPSE (cm)	1.697 (0.156–18.425)	0.664	0.943 (0.242–3.672)	0.932
PDEI	1.366 (0.562–3.317)	0.491	0.830 (0.324–2.129)	0.699
Prostanoid	0.736 (0.348–1.553)	0.421	1.922 (0.790–4.674)	0.151
ERA	1.209 (0.356–4.104)	0.761	0.650 (0.140–3.021)	0.583
Dopamine	4.079 (0.773–21.535)	0.098	1.881 (0.547–6.469)	0.316
Dobutamine	2.364 (1.122–4.981)	0.024	1.937 (0.775–5.021)	0.154
Milrinone	0.941 (0.110–8.631)	0.981	1.618 (0.181–14.491)	0.667

Abbreviations: ALT, alanine transaminase; CI, confidence interval; CO, cardiac output; CR, creatinine; DBP, diastolic blood pressure; DE, Doppler echocardiography; ERA, endothelin receptor antagonist; HR, heart rate; mPAP, mean pulmonary artery hypertension; mRAP, mean right atrium pressure; NT-proBNP, N-terminal pro-Btype natriuretic peptide; OR, odds ratio; PDEI, Phosphodiesterase type-5 inhibitors; PVR, periphery vessel resistance; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.
The unadjusted hazard ratios (95% CIs) for risk of hospital mortality.

Table 3 Multivariate-adjusted OR for 30-day re-hospitalization and in-hospital mortality.

	30-day re-hospitalization		*In-hospital mortality*	
	OR (95%CI)	P *value*	*OR (95%CI)*	P *value*
WHO-FC	—	—	21.236 (6.916–65.202)	<0.001
Group (fasudil/no fasudil)	0.214 (0.063–0.733)	0.014	0.141 (0.036–0.549)	0.005
Dobutamine	2.613 (1.011–4.628)	0.047	—	—

Abbreviations: CI, confidence interval; OR, odds ratio; WHO-FC, World Health Organization functional class.
The multivariate-adjusted hazard ratios (95% CIs) for risk of hospital mortality. Abbreviations as in Table 1.

2006, Ishikura and colleagues[22] described eight patients with PAH who were treated using the same fasudil regimen. There was statistically significant improvement in total peripheral resistance, mPAP and CI. The total peripheral resistance/systematic vessel resistance (SVR) ratio exhibited a decrease that was not statistically significant. In 2009, Li *et al.*[24] studied 12 pediatric patients scheduled for shunt closure. A dose of 30 mg of fasudil over 30 min resulted in a 33% reduction in PVR, and there was a non-significant 23.9% reduction in the PVR/SVR ratio. Fujita *et al.*[23] found that fasudil resulted in statistically significant reductions in mPAP and the PVR/SVR ratio as well as in the level of nitric oxide. More recently, Fukumoto and colleagues[27] described the first double-blinded, placebo-controlled trial with oral fasudil in PAH patients. The results of mid-term treatment with fasudil demonstrated an improvement in CI compared with placebo.

We did not collect hemodynamic or molecular biological data for elucidating the mechanisms responsible for the favorable effects of fasudil in our study, but we surmised that the effects on the hemodynamics and molecular biology of PH patients—supported by the above studies—may contribute to reductions in the rates of both in-hospital mortality and 30-day re-hospitalization.

The selectivity of fasudil for the pulmonary arterial bed suggests that it may play a role in the management of critically ill hospitalized patients with PH. A common clinical challenge faced by clinicians involves instituting effective therapy without exacerbating systemic vasodilatation.

RAP, PAP, PVR, CO and N-terminal pro-B type natriuretic peptide are important prognostic factors of mortality in PAH; a predictive relationship between these parameters and mortality has been reproduced in many studies.[32–35] However, in our study, RAP, PAP, PVR and CO were not associated with in-hospital mortality ($P>0.05$). We believe that there are two reasons for this finding. First, in-hospital mortality was a short-term prognosis rather than a long-term prognosis. The observation time may have been too short to influence mortality in patients with acute RHF and PH patients classified as

Table 4 The safety of i.v. fasudil hydrochloride

	Baseline	*After treatment*	P *value*
RBC ($\times10^{12}$ l^{-1}) ($n=43$)	4.82 ± 0.93	4.67 ± 0.73	0.121
WBC ($\times10^{9}$ l^{-1}) ($n=43$)	6.25 (5.23, 8.40)	7.20 (5.50, 9.30)	0.170
PLT ($\times10^{9}$ l^{-1}) ($n=43$)	160.14 ± 63.83	177.86 ± 78.85	0.051
ALT (IU l^{-1}) ($n=49$)	18.50 (14.00, 30.00)	22.00 (15.00, 33.00)	0.083
AST (IU l^{-1}) ($n=49$)	26.00 (20.00, 34.25)	28.39 ± 9.73	0.917
Cr (μmol l^{-1}) ($n=45$)	60.00 (48.75, 73.00)	65.00 (52.00, 77.00)	0.491
BUN (mmol l^{-1}) ($n=45$)	6.17 ± 2.21	6.20 (5.35, 8.00)	0.445

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; PLT, blood platelet.
Values are expressed as *n* (%) or mean ± s.d. or median (25th, 75th percentiles).

WHO-FC III or WHO-FC IV; RAP, PAP, PVR and CO may have diminished the impact of the other parameters on patients' short-term prognoses.

The second reason stems from the fact that dobutamine plays a more important role in RV contractility than dopamine.[36–40] In our center, only 20.4–36.4% of the patients were treated with dobutamine; most of the patients received dopamine (Table 1) owing to low blood pressure. We did not have enough previous experience regarding this issue. Now, however, dobutamine is the first line of inotropic therapy for PH patients in our center.

Study limitations

This study did not standardize the background treatment approaches to acute RHF; therefore, there may have been better or poor care provided to the groups. Additionally, differences in time collection may have introduced the following confounders: (i) patient severity bias, (ii) improved diagnostic techniques and treatments during a more recent treatment period and (iii) differences in data integrity and follow-up between different treatment periods. Some of the patients did not undergo RHC in this study. Of these, 15 patients with PH had undergone an RHC several years previously at our center and did not undergo a repeat procedure during this study. Because it was not appropriate to use their hemodynamic parameters to analyze their risk factors for disease mortality, we did not analyze the hemodynamic parameters of these patients. Three patients were diagnosed via an RHC after recovering and returning for a follow-up visit. Patients who did not undergo an RHC were diagnosed with PH according to their symptoms, signs, history suggestive of PH and echocardiographic findings. This was a limitation of our study. However, the focus of our study was severe RHF as opposed to PAH. Therefore, the lack of RHC data was acceptable because it is difficult for PH patients with severe RHF to undergo an RHC. We will devote more attention to this problem in future studies.

Our study was a short-term study rather than a long-term study. Medication administered during hospitalization will only affect a patient's short-term prognosis; it cannot influence the long-term outcome, which may be affected by many factors. Therefore, we did not include follow-up hemodynamic and echocardiographic data in our study. The primary clinical outcomes in our study were in-hospital mortality and 30-day re-hospitalization for cardiovascular symptoms. Information regarding re-hospitalization was obtained either during follow-up or via telephone interview. We did not assess secondary outcome measures such as serum markers or echocardiography, and we recognize that this may represent another limitation of our study. We will design more comprehensive studies in the future.

CONCLUSION

Rho-kinase inhibitors are a promising new class of drugs for the treatment of PH and acute RHF. Intravenous fasudil appears to be safe and may reduce the rates of both in-hospital mortality and re-hospitalization among these patients. This report represents another step toward even more effective treatments for a deadly disease. However, a prospective trial, with a standardized background protocol, is needed.

CONFLICT OF INTEREST

Dr Z-C Jing serves as a consultant and scientific advisor to Actelion, Bayer Schering, AstraZeneca, Pfizer and United Therapeutics, in addition to being an investigator in trials sponsored by these companies. Actelion, Gilead, Medtronic, Novartis, Lung Biotechnology, Reata, and Ventripoint have provided funding to the University of Chicago to support Dr Gomberg-Maitland's conduct of clinical trials. Dr Gomberg-Maitland has served as a consultant for Actelion, Bayer, Gilead, Medtronic, Bellerophon (formerly known as Ikaria) and United Therapeutics, as a member of steering committees and DSMB/event committees. She has received honoraria for CME from Medscape and ABComm. Dr Gomberg-Maitland is a member of the PCORI Advisory Panel on Rare Diseases and a Special Government Employee in the FDA's Cardio-Renal Division. The other authos declare no conflict of interest.

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1 Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997; **336**: 111–117.
2 Rabinovitch M. Pulmonary hypertension: updating a mysterious disease. *Cardiovasc Res* 1997; **34**: 268–272.
3 Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; **351**: 1425–1436.
4 Hirashiki A, Kondo T, Murohara T. Combination therapy adding tadalafil to existing ambrisentan in patients with pulmonary arterial hypertension. *Hypertens Res* 2014; **37**: 488–489.
5 Zhuang Y, Jiang B, Gao H, Zhao W. Randomized study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertens Res* 2014; **37**: 507–512.
6 Schermuly RT, Janssen W, Weissmann N, Stasch JP, Grimminger F, Ghofrani HA. Riociguat for the treatment of pulmonary hypertension. *Expert Opin Investig Drugs* 2011; **20**: 567–576.
7 Guo Q, Huang JA, Yamamura A, Yamamura H, Zimnicka AM, Fernandez R, Yuan JX. Inhibition of the Ca(2+)-sensing receptor rescues pulmonary hypertension in rats and mice. *Hypertens Res* 2014; **37**: 116–124.
8 Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, Housten T, Lechtzin N, Chami H, Girgis RE, Hassoun PM. Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension. *Eur Respir J* 2011; **38**: 359–367.
9 Sztrymf B, Souza R, Bertoletti L, Jais X, Sitbon O, Price LC, Simonneau G, Humbert M. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J* 2010; **35**: 1286–1293.
10 Haddad F, Peterson T, Fuh E, Kudelko KT, de Jesus PV, Skhiri M, Vagelos R, Schnittger I, Denault AY, Rosenthal DN, Doyle RL, Zamanian RT. Characteristics and outcome after hospitalization for acute right heart failure in patients with pulmonary arterial hypertension. *Circ Heart Fail* 2011; **4**: 692–699.
11 Fukumoto Y, Shimokawa H. [The role of Rho-kinase pathway on PAH]. *Nihon Rinsho* 2008; **66**: 2091–2096.
12 Fukumoto Y, Tawara S, Shimokawa H. Recent progress in the treatment of pulmonary arterial hypertension: expectation for rho-kinase inhibitors. *Tohoku J Exp Med* 2007; **211**: 309–320.
13 Takemoto M, Sun J, Hiroki J, Shimokawa H, Liao JK. Rho-kinase mediates hypoxia-induced downregulation of endothelial nitric oxide synthase. *Circulation* 2002; **106**: 57–62.
14 Hyvelin JM, Howell K, Nichol A, Costello CM, Preston RJ, McLoughlin P. Inhibition of Rho-kinase attenuates hypoxia-induced angiogenesis in the pulmonary circulation. *Circ Res* 2005; **97**: 185–191.
15 Ward JP, McMurtry IF. Mechanisms of hypoxic pulmonary vasoconstriction and their roles in pulmonary hypertension: new findings for an old problem. *Curr Opin Pharmacol* 2009; **9**: 287–296.

16 Li FH, Xia W, Li AW, Zhao CF, Sun RP. Inhibition of rho kinase attenuates high flow induced pulmonary hypertension in rats. *Chin Med J (Engl)* 2007; **120**: 22–29.
17 Li F, Xia W, Li A, Zhao C, Sun R. Long-term inhibition of Rho kinase with fasudil attenuates high flow induced pulmonary artery remodeling in rats. *Pharmacol Res* 2007; **55**: 64–71.
18 Nohria A, Grunert ME, Rikitake Y, Noma K, Prsic A, Ganz P, Liao JK, Creager MA. Rho kinase inhibition improves endothelial function in human subjects with coronary artery disease. *Circ Res* 2006; **99**: 1426–1432.
19 Hirooka Y, Shimokawa H. Therapeutic potential of rho-kinase inhibitors in cardiovascular diseases. *Am J Cardiovasc Drugs* 2005; **5**: 31–39.
20 Abe K, Shimokawa H, Morikawa K, Uwatoku T, Oi K, Matsumoto Y, Hattori T, Nakashima Y, Kaibuchi K, Sueishi K, Takeshit A. Long-term treatment with a Rho-kinase inhibitor improves monocrotaline-induced fatal pulmonary hypertension in rats. *Circ Res* 2004; **94**: 385–393.
21 Fagan KA, Oka M, Bauer NR, Gebb SA, Ivy DD, Morris KG, McMurtry IF. Attenuation of acute hypoxic pulmonary vasoconstriction and hypoxic pulmonary hypertension in mice by inhibition of Rho-kinase. *Am J Physiol Lung Cell Mol Physiol* 2004; **287**: L656–L664.
22 Ishikura K, Yamada N, Ito M, Ota S, Nakamura M, Isaka N, Nakano T. Beneficial acute effects of rho-kinase inhibitor in patients with pulmonary arterial hypertension. *Circ J* 2006; **70**: 174–178.
23 Fujita H, Fukumoto Y, Saji K, Sugimura K, Demachi J, Nawata J, Shimokawa H. Acute vasodilator effects of inhaled fasudil, a specific Rho-kinase inhibitor, in patients with pulmonary arterial hypertension. *Heart Vessels* 2010; **25**: 144–149.
24 Li F, Xia W, Yuan S, Sun R. Acute inhibition of Rho-kinase attenuates pulmonary hypertension in patients with congenital heart disease. *Pediatr Cardiol* 2009; **30**: 363–366.
25 Fukumoto Y, Matoba T, Ito A, Tanaka H, Kishi T, Hayashidani S, Abe K, Takeshita A, Shimokawa H. Acute vasodilator effects of a Rho-kinase inhibitor, fasudil, in patients with severe pulmonary hypertension. *Heart* 2005; **91**: 391–392.
26 Do EZ, Fukumoto Y, Takaki A, Tawara S, Ohashi J, Nakano M, Tada T, Saji K, Sugimura K, Fujita H, Hoshikawa Y, Nawata J, Kondo T, Shimokawa H. Evidence for Rho-kinase activation in patients with pulmonary arterial hypertension. *Circ J* 2009; **73**: 1731–1739.
27 Fukumoto Y, Yamada N, Matsubara H, Mizoguchi M, Uchino K, Yao A, Kihara Y, Kawano M, Watanabe H, Takeda Y, Adachi T, Osanai S, Tanabe N, Inoue T, Kubo A, Ota Y, Fukuda K, Nakano T, Shimokawa H. Double-blind, placebo-controlled clinical trial with a rho-kinase inhibitor in pulmonary arterial hypertension. *Circ J* 2013; **77**: 2619–2625.
28 Jiang BH, Tawara S, Abe K, Takaki A, Fukumoto Y, Shimokawa H. Acute vasodilator effect of fasudil, a Rho-kinase inhibitor, in monocrotaline-induced pulmonary hypertension in rats. *J Cardiovasc Pharmacol* 2007; **49**: 85–89.
29 Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, Yuan P, Jiang X, He J, Humbert M, Jing ZC. Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. *Chest* 2011; **140**: 301–309.
30 Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**: D42–D50.
31 Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; **30**: 2493–2537.
32 Fijalkowska A, Kurzyna M, Torbicki A, Szewczyk G, Florczyk M, Pruszczyk P, Szturmowicz M. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest* 2006; **129**: 1313–1321.
33 Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; **102**: 865–870.
34 Chapman PJ, Bateman ED, Benatar SR. Prognostic and therapeutic considerations in clinical primary pulmonary hypertension. *Respir Med* 1990; **84**: 489–494.
35 Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galie N. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54**: S78–S84.
36 Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med* 2011; **183**: 847–855.
37 Holloway EL, Polumbo RA, Harrison DC. Acute circulatory effects of dopamine in patients with pulmonary hypertension. *Br Heart J* 1975; **37**: 482–485.
38 Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, Naeije R, Brimioulle S. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. *Crit Care Med* 2004; **32**: 1035–1040.
39 Chen EP, Bittner HB, Davis RJ, Van Trigt PR. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. *Ann Thorac Surg* 1997; **63**: 814–821.
40 Poor HD, Ventetuolo CE. Pulmonary hypertension in the intensive care unit. *Prog Cardiovasc Dis* 2012; **55**: 187–198.