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Original Article

Safety and efficacy of urapidil and nitroglycerin in the treatment of elderly patients with acute heart failure: a randomized multi-center parallel-control study in China

Jingyu He[1], Jing Wang[1], Yujie Zhou[2], Yan Fu[3], Jian Qin[1], Shu Qin[4], Xiaomin Chen[5], Jincheng Guo[6], Dezhao Wang[7], Hong Zhan[8], Wei Guan[9], Yawei Xu[10], Qi Hua[1]

[1]Emergency Department, Xuanwu Hospital, Capital Medical University, Beijing, China; [2]Department of Cardiology, Beijing Anzhen Hospital Affiliated to Capital Medical University, Beijing, China; [3]Emergency Department, Tongren Hospital Affiliated to Capital Medical University, Beijing, China; [4]Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; [5]Department of Cardiology, Ningbo No. 1 Hospital, Ningbo, Zhejiang, China; [6]Department of Cardiology, Luhe Hospital Affiliated to Capital Medical University, Beijing, China; [7]Department of Cardiology, Mentougou District Hospital of Beijing, Beijing, China; [8]Department of Emergency, The First Hospital Affiliated of Sun Yat-sen Medical University, Guangzhou, Guangdong, China; [9]Department of Cardiology, Heilongjiang Provincial People's Hospital, Harbin, Heilongjiang, China; [10]Department of Cardiology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, China

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Abstract: The aim of this study was to compare the efficiency and safety of urapidil and nitroglycerin in treating elderly patients with acute heart failure. A total of 248 patients with acute heart failure were recruited randomly from 10 clinical centers. In this article, efficiency of medication to elderly patients (age ≥60 yrs., n = 222) was specially focused. Patients were administrated with urapidil (n = 107) or nitroglycerin (n = 115) by micro-pump continuously for 48 hours. Compared with nitroglycerin, urapidil significantly increased ejection fraction (EF%), decreased left ventricular end diastolic volume (EDV) and end systolic volume (ESV). No significant difference of NT-pro BNP was detected (2-day: ESV, P = 0.067; EDV, P = 0.016; EF%, P = 0.054; NT-pro BNP, P = 0.853; 7-day: ESV, P = 0.039; EDV, P = 0.054; EF%, P = 0.035; NT-pro BNP, P = 0.931); Urapidil provided significantly lipid-decreasing effects, and showed no disadvantage effects on blood glucose (⊿2d: cholesterol, P = 0.016; LDL, P = 0.031; blood glucose, P = 0.613; ⊿7d: cholesterol, P = 0.012; LDL, P = 0.059; blood glucose, P = 0.422); More severely deteriorated baseline renal function was observed in urapidil group (P = 0.024), however, the increase amplitude of creatinine was comparable at all tested time points between the two groups (⊿2d: P = 0.692; ⊿7d: P = 0.742); And 30-day incidence of re-hospitalization and deterioration of cardiac function was significantly lower in urapidil group (P = 0.046). Therefore, urapidil more effectively reduces cardiac load and improves cardiac function, while providing more significant protection to renal function and improving blood lipid metabolism. We recommended that urapidil should be preferably used for elderly patients with acute heart failure as an effective and safe vasodilator.

Keywords: Urapidil, acute heart failure, nitroglycerin, elderly patients

Introduction

With the acceleration of the population aging and the rise in the incidence of cardiovascular and cerebrovascular diseases, the morbidity and prevalence of heart failure has increased year by year, congestive heart failure in elder patients is often complicated with comorbidities, such as: coronary heart disease, hypertension, diabetes and renal failure. A variety of factors causing heart failure act interactively and directly inhibit myocardial contraction and energy metabolism. Triggered by incentives, such as: infection and emotional fluctuations, heart failure in elder patients is usually featured by rapid onset and progress, high mortality and morbidity. The synthetic action of a variety of factors leads to heart failure, severely threatening the patients' life [1].

Vasodilator has been widely used as classic medication treating heart failure in acute stage

by relieving peripheral vascular spasm, immediately correcting hemodynamic disorder, and relieving the patents' symptoms [2]. Nitrates (including nitroglycerin and nitroprusside) have been used as classic vasodilators treating acute decompensated heart failure for nearly a century for such purpose. Nitrates immediately reduce cardiac load, improve blood supply of coronary artery and relieve patients' heart failure symptom by targeting nitric ester receptor and prostaglandin receptor in vascular smooth muscle. However, the rapid development of clinical drug resistance and adverse effects (such as: headache and increased intraocular pressure) also significantly limit its use in elderly patients [3]. Urapidil is a novel vasodilator that can effectively reduce cardiac pre-and after-load and pulmonary circulation resistance through the dual action of both central and peripheral vasorelaxation. Few reports of clinical drug resistance have been reported previously. Its rapid and significant antihypertensive effect makes it a frequent choice for treating hypertensive crisis, preoperative or postoperative hypertension, and preeclampsia, which have been supported with significant clinical benefits [4]. It has been used clinically to treat right ventricular dysfunction due to its significant effect of reducing pulmonary circulation resistance, relieving pulmonary artery hypertension of structural lung diseases such as COPD [5]. Although urapidil has been recommended to treat acute heart failure by Chinese experts as IIA drugs according to 2010 Diagnosis and Treatment Guideline for Acute Heart Failure, its clinical application treating acute left heart failure has been rarely reported [6, 7]. Meanwhile, urapidil has been recommended for hemodynamic management of heart failure in patients with hypertension [8]. However, the clinical practice currently has been limited due to lack of medical evidence from large sample and multi-center evidence-based medicine. Therefore, the multi-center parallel-control and randomized study is designed to compare hemodynamic changes, safety and efficacy of urapidil and nitroglycerin in the treatment of Chinese elderly patients with acute heart failure.

Patients and methods

Subjects

MUSE study was registered in Chinese Clinical Trial Registry (Chi-CTR) with registration number of ChiCTR-11001781.

Adult patients admitted from August 2011 to November 2013 in 10 study centers of China (including: Department of Cardiology and Emergency Department, Xuanwu Hospital, Capital Medical University; Department of Cardiology, Beijing Anzhen Hospital affiliated to the Capital Medical University; Emergency Department of Tongren Hospital affiliated to the Capital Medical University; Department of Cardiology of the First Affiliated Hospital of Chongqing Medical University; Department of Cardiology of Ningbo No. 1 Hospital; Department of Cardiology of Luhe Hospital of Beijing Tongzhou District; Department of Cardiology of Mentougou District Hospital of Beijing; Emergency Department of The First Hospital Affiliated of Sun Yat-sen Medical University; Department of Cardiology of Heilongjiang Hospital; Department of Cardiology of Shanghai Tenth People's Hospital affiliated to Tongji University) were for MUSE study. Patients were randomly assigned to nitroglycerin group and urapidil group according to digital table method in a parallel and competitive way. At the end of study, a total of 248 eligible cases were recruited from all sites, including 125 male patients and 123 female patients. The average age of nitroglycerin group (125 cases, male to female ratio of 64/61) and urapidil group (123 cases, male to female ratio of 61/62) respectively were 70.73±11.27 yrs. and 69.27±12.84 yrs (P = 0.902). This study focused on efficacy and safety in heart failure of urapidil and nitroglycerin for elder patients (age ≥60 yrs.): 115 cases (male to female of 55/60, with average age of 74.71±6.99 yrs.) and 107 cases (male to female of 52/55, with average age of 74.55±7.23 yrs.) respectively for nitroglycerin and urapidil groups.

Inclusion criteria: (1) Age ≥60 yrs.; (2) Diagnosis as acute heart failure; (3) New York Heart Association (NYHA) classification ≥ Class II or Killip classification ≥ Class II; Heart failure with systolic blood pressure (SBP) at admission ≥110 mmHg (1 mmHg = 0.133 kpa); (4) Patients with history of hypertension; (5) Sign the informed consent. This study was reviewed by the ethics committee of all hospitals. The planning and implementation of clinical trials followed the applicable national laws; the implementation of the trial complied with the Helsinki declaration and the ethical standards of GCP.

Exclusion criteria: (1) Patients with cardiac shock or other contraindications during clinical application of intravenous vasodilator; (2)

Table 1. Baseline characteristics of Nitroglycerin and Urapidil group

	Nitroglycerin (n = 115)	Urapidil (n = 107)	*P* value
Age (years)	74.71±6.99	74.55±7.23	0.875
Gender (male%)	55 (47.8%)	52 (48.6%)	0.908
BMI (kg/m^2)	24.71±4.04	25.12±4.23	0.477
Medical history			
Smoking	38 (33.3%)	34 (31.8%)	0.803
Drinking	17 (14.8%)	17 (15.9%)	0.856
Diabetes	41 (35.7%)	38 (35.5%)	0.983
Coronary heart disease	60 (52.2%)	66 (61.7%)	0.153
Cerebral vascular disease	13 (11.3%)	18 (16.8%)	0.236
Atrial fibrillation	13 (11.3%)	15 (14.0%)	0.543
COPD	12 (10.4%)	11 (10.3%)	0.970
Hyperlipidemia	53 (46.1%)	49 (45.8%)	0.965
Metabolic syndrome	63 (54.8%)	65 (60.7%)	0.369
Classification of heart failure			
Killip classification	62 (53.9%)	51 (47.7%)	0.352
II [cases (%)]	32 (27.8%)	22 (20.6%)	0.207
III [cases (%)]	10 (8.7%)	9 (8.4%)	0.940
IV [cases (%)]	20 (17.4%)	20 (18.7%)	0.801
NYHA classification	53 (46.1%)	56 (52.3%)	0.352
II [cases (%)]	15 (13.0%)	7 (6.5%)	0.158
III [cases (%)]	15 (13.0%)	10 (9.3%)	0.384
IV [cases (%)]	35 (30.4%)	39 (36.4%)	0.342
Cause of heart failure			
Coronary heart disease	85 (73.9%)	82 (76.6%)	0.494
Hypertension	17 (14.8%)	10 (9.3%)	0.216
Atrial fibrillation	8 (7.0%)	9 (8.4%)	0.684
Cardiomyopathy or others	5 (4.3%)	6 (5.6%)	0.666
Lab test			
WBC count (10^{12}/L)	8.39±3.34	8.57±3.22	0.679
Neutrophils (10^{12}/L)	5.97±2.94	6.38±3.15	0.336
Hemoglobin (g/L)	126.72±20.07	128.06±22.34	0.638
K^+ (mmol/L)	4.12±0.49	4.12±0.50	0.901
Na^+ (mmol/L)	140.41±4.59	140.13±5.40	0.680
HCY (μmol/L)	21.40±14.27	21.73±13.74	0.901
hsCRP (mg/L)	14.99±21.67	15.18±18.51	0.950

Data are presented as the mean ± standard deviation or n (%). BMI, body mass index; COPD, chronic obstructive pulmonary disease; HCY, homocysteine; hs-CRP, hypersensitive C reaction protein.

Severe valvular heart disease (rheumatic heart disease, calcified valvular disease), hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy or constrictive pericarditis, acute attack of severe chronic asthmatic bronchitis and pulmonary disease; (3) Severe liver and renal insufficiency: Alanine aminotransferase (ALT) or-/and- Aspartate aminotransferase (AST) ≥3 times of the normal upper limit, serum creatinine (SCR) ≥ twice of the normal upper limit; (4) Known or suspected of being allergic to study medicines or any of their ingredients; (5) Considered unsuitable to be included in this study (with tumor or mental disorders) by investigators; (6) Having used other study medicines or having been involved in other clinical trials or studies within 60 days of recruitment; (7) Experience of participating in this study.

Treatment methods: Patients were assigned to urapidil and nitroglycerin groups with random envelope process after admission. In addition to standard heart failure treatment, subjects of urapidil group were treated with urapidil hydrochloride injection (brand name EbrantilR, specification of 5 ml: 25 mg, made by Japan Takeda Pharmaceutical Co. Ltd.). 100 mg urapidil and 30 ml 0.9% sodium chloride injection were loaded into 50 ml micro-pump; administrated starting with minimal clinical dosage (25 μg/min) based on the clinical condition and adjusted every 15 min according to blood pressure. Target volume of urapidil injection (50 or 100 μg/min) should be dropped within 6 hrs. Maximum dosage of urapidil was 400 μg/min and blood pressure should be maintained >90/60 mmHg. Subjects of nitroglycerin received nitroglycerin (specification: 1 ml: 5 mg, made by Beijing Yimin pharmaceutical). 10 mg nitroglycerin and 48 ml 0.9% sodium chloride injection were loaded into 50 ml micro-pump. Administration started with minimal dosage (2.5 μg/min) based on the clinical condition and adjusted every 15 min according to blood pressure. Target volume of injection (5 or 10 μg/min) should be dropped

Table 2. Heamodynamic trajectories between Nitroglycerin and Urapidil groups

	Groups	Baseline	24 hours	48 hours	72 hours	7 days
SBP	Nitroglycerin	152.52±31.07	133.04±23.87	129.38±20.14	126.68±17.61	122.17±14.61
	Urapidil	160.30±31.01*	134.68±18.21	129.55±16.07	130.15±16.71	125.10±12.02
DBP	Nitroglycerin	82.93±17.66	71.64±12.99	69.38±11.47	67.52±10.65	68.44±10.06
	Urapidil	87.01±20.70*	73.17±13.96	71.18±12.42	70.99±11.53	70.22±10.91
HR	Nitroglycerin	85.31±19.90	77.19±15.60	76.60±14.17	73.13±12.27	72.13±11.96
	Urapidil	87.35±20.69	79.97±16.62	77.70±15.38	75.90±10.85	73.49±9.81

Data are presented as the mean ± standard deviation, *P<0.05. SBP, systolic and diastolic blood pressure; DBP, diastolic blood pressure; HR, heart rates.

within 6 hrs. with maximal dosage of 20 μg/min to maintain the blood pressure >90/60 mmHg. No other vasodilator was given during the overall dosage duration (48 hrs.). The drug use and combined medication were recorded for each group.

Observation indicators

The pre-treatment (baseline), 1 day, 2 days, 3 days, and 7 days post treatment condition of all cases were observed, including the change in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rates (HR) and N-terminal B type natriuretic peptide (NT pro-BNP) indicative of cardiac function [9]. Changes of liver, renal function, blood glucose and lipid levels were observed before treatment, 2 days and 7 days after treatment. Meanwhile, echocardiography was performed repeatedly to evaluate ESV EDV and EF. Combined medicines and adverse events should be recorded timely, as well as major adverse cardiovascular events (MACEs) during follow-up and 30 days after completion of study, including sudden cardiac death, non-fatal myocardial infarction, malignant arrhythmia, re-hospitalization or-/and-deterioration of cardiac function.

Statistical analysis

The results were analyzed using SPSS software (Version 21.0, SPSS Chicago, USA) for normality test. The measurement data were expressed by mean ± standard deviation and were analyzed using Student *t* test, and the counting data were expressed by percentage and were subject to Chi-square test. Multivariate analysis of variance through General Linear Model was applied to analyze the repeated data at unequal intervals and observe the changes of blood pressure (SBP, DBP), heart rate (HR), cardiac function (NT-pro BNP), biochemical indicators (bloods glucose, blood lipid, renal and hepatic function) as well as echocardiography parameters of two groups at different time points were compared. There was statistical significance when P<0.05.

Results

*Basic data analysis (**Table 1**)*

Complications were common in elder patients enrolled in the study, including coronary heart disease (75.2%), heart failure after myocardial infarction (50.9%), diabetes (35.6%), hyperlipidemia (45.9%); metabolic syndrome (57.6%). Gender and age distribution, complications, causes of heart failure, heart failure classifications, and lab test results were comparable between two groups, and there was no statistical significance (P>0.05).

*Comparison between two groups of hemodynamic parameters at different time points before and after treatment (**Table 2**)*

SBP and DBP at all post-treatment time points for patients in both nitroglycerin and urapidil-treated groups reduced (P<0.05, intra-group comparison); heart rate for patients of both groups showed the trend of decline with improvement of heart failure (P<0.05, intra-group comparison). No reflex tachycardia was observed in both groups.

Comparison between groups of corrected serum creatinine showed that baseline blood pressure of urapidil group was significantly higher than nitroglycerin group (SBP of urapidil vs. nitroglycerin: 160.30±31.01 vs. 152.52± 31.07 mmHg, P = 0.003; DBP: 87.01±20.70 vs. 82.93±17.66 mmHg, P = 0.034). There was no

Table 3. The Changes of Cardiac Structure and Functions between Nitroglycerin and urapidil group

	Nitroglycerin (n = 115)	Urapidil (n = 107)	*P* value
NT pro-BNP (pg/ml)			
Before treatment	6142.86±7575.71	6178.63±7822.19	0.977
2 days after treatment	4034.77±5664.94	3868.30±5268.18	0.853
7 days after treatment	2686.34±5377.64	2615.37±4787.80	0.931
P value	<0.001*	<0.001*	
EF (%)			
Before treatment	49.79±10.95	50.94±8.90	0.253
2 days after treatment	50.50±11.13.	52.09±11.41	0.054
7 days after treatment	52.51±12.56	56.74±11.48	0.035*
P value	0.019*	0.005*	
ESV (ml)			
Before treatment	80.83±42.79	75.23±42.69	0.220
2 days after treatment	83.05±44.91	71.36±40.72	0.067
7 days after treatment	80.36±43.74	67.69±39.11	0.039*
P value	0.453	0.035*	
EDV (ml)			
Before treatment	152.27±54.69	150.27±54.89	0.452
2 days after treatment	156.68±56.42	139.61±52.08	0.016*
7 days after treatment	145.44±47.61	140.93±53.10	0.054
P value	0.143	0.027*	

Data are presented as the mean ± standard deviation. *P<0.05. EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume.

significant difference in blood pressure between the two groups at each time point after admission (1 day, 2 days, 3 days and 7 days after admission: SBP: P = 0.531, 0.829, 0.212, 0.848; DBP: P = 0.366, 0.429, 0.847, 0.992); after 48 hours of continuous use, the systolic pressure of urapidil group decreased significantly than that of nitroglycerin group (urapidil vs. nitroglycerin: ⊿2d SBP: 30.69±26.91 vs. 23.82±23.48, P = 0.034; ⊿2d DBP: 14.79± 17.94 vs. 12.51±15.94, P = 0.294).

There was no statistical difference in heart rate between the two groups (P>0.05).

*Comparison of cardiac structure and function between the two groups before and after treatment (**Table 3**)*

NT Pro-BNP levels for nitroglycerin and urapidil groups decreased while EF increased at each time point (P<0.05). Meanwhile, improvement of ESV and EDV were observed in urapidil-treated patients with statistical difference for intragroup comparison (ESV (ml): 75.23±42.69 vs. 71.36±40.72 vs. 67.69± 39.11, P = 0.035; EDV (ml): 150.27±54.89 vs. 139.61± 52.08 vs. 140.93±53.10, P = 0.027); while for the nitroglycerin group, EDV and ESV were not statistically different at each time point (P>0.05).

EF, EDV and ESV were not significantly different between the two groups at admission. Comparison between groups for corrected serum creatinine and mean arterial pressure showed that on 7th day after treatment, EF of urapidil group was significantly higher than that of nitroglycerin group (urapidil vs. nitroglycerin: 56.74±11.48 vs. 52.51± 12.56, P = 0.035), while EDV and ESV of urapidil group were lower than that of nitroglycerin group (on 2nd day after treatment, urapidil vs. nitroglycerin: EDV: 156.68±56.42 vs. 139.61±52.08, P = 0.016; on 7th day after treatment: ESV: 80.36±43.74 vs. 67.69±39.11, P = 0.039).

*Comparison of changes of creatinine, glucose and lipid metabolism of patients in two groups (**Table 4**)*

Comparison between groups showed that creatinine level of urapidil group at each time point was significantly higher than that of nitroglycerin group. Further analysis of creatinine change trends showed that creatinine increase amplitude at all time points were similar between the two groups (urapidil vs. nitroglycerin: ⊿2d: 5.66±23.19 vs. 4.19±31.21, P = 0.692; ⊿7d: 7.37±34.89 vs. 5.52±40.75, P = 0.74). No aggravation of renal function was observed in urapidil-treated group.

Cholesterol and low density lipoprotein levels of urapidil group at each time point were higher than nitroglycerin group (P<0.05). Triglyceride and high density lipoprotein levels were not significantly different between the two groups at

Table 4. Comparison of creatinine and glucose and lipid metabolism between Nitroglycerin and Urapidil groups

Characteristics	Nitroglycerin (n = 115)	Urapidil (n = 107)	*P* value
SCR (μmol/L)			
Before treatment	90.58±48.11	107.68±47.48	0.024*
2 days after treatment	96.58±52.07	113.39±51.28	0.036*
7 days after treatment	96.24±55.76	114.71±57.78	0.035*
P value	0.171	0.089	
⊿2d	4.19±31.21	5.66±23.19	0.692
⊿7d	5.52±40.75	7.37±34.89	0.742
TCHO (mmol/L)			
Before treatment	4.01±1.06	4.84±1.52	0.001*
2 days after treatment	3.96±0.92	4.42±1.30	0.024*
7 days after treatment	3.99±1.01	4.43±1.31	0.036*
P value	0.886	0.020*	
⊿2d	0.023±0.75	-0.30±0.96	0.016*
⊿7d	-0.06±0.96	-0.33±1.32	0.012*
LDL (mmol/L)			
Before treatment	2.36±0.79	3.16±1.23	<0.001*
2 days after treatment	2.27±0.74	2.84±1.13	0.006*
7 days after treatment	2.47±0.90	2.81±1.03	0.095
P value	0.217	0.022*	
⊿2d	-0.027±0.64	-0.26±0.74	0.031*
⊿7d	0.031±0.80	-0.3±1.01	0.059
TG (mmol/L)			
Before treatment	1.45±1.23	1.39±0.69	0.658
2 days after treatment	1.28±0.54	1.42±0.63	0.183
7 days after treatment	1.43±0.67	1.43±0.59	0.980
P value	0.101	0.556	
⊿2d	-0.086±0.82	0.074±0.53	0.104
⊿7d	-0.003±1.02	0.074±0.49	0.570
HDL (mmol/L)			
Before treatment	1.18±0.28	1.40±0.71	0.066
2 days after treatment	1.10±0.27	1.24±0.40	0.060
7 days after treatment	1.12±0.25	1.16±0.31	0.502
P value	0.030	0.004*	
⊿2d	-0.064±0.20	-0.13±0.55	0.271
⊿7d	-0.10±0.29	-0.23±0.55	0.141
Fasting blood glucose (mmol/L)			
Before treatment	8.01±4.0	8.37±5.37	0.643
2 days after treatment	7.43±3.45	7.30±2.92	0.831
7 days after treatment	6.93±3.29	6.60±2.26	0.492
P value	0.042*	0.027*	
⊿2d	-0.41±4.11	-0.70±4.13	0.613
⊿7d	-1.07±3.73	-1.64±5.15	0.422

Data are presented as the mean ± standard deviation. *P<0.05. ⊿2d = 2 days data after treatment-baseline data; ⊿7d = 7 days data after treatment-baseline data; SCR: creatine; TCHO: cholesterol; LDL: low density lipoprotein; TG: triglyceride; HDL: high density lipoprotein.

different time points. Comparison of blood lipid level change between the two groups at each time point showed that urapidil was more conducive to decrease blood lipid than nitroglycerin (urapidil vs. nitroglycerin: Cholesterol: ⊿2d: -0.30±0.96 vs. 0.023±0.75, P = 0.016; ⊿7d: -0.33±1.32 vs. -0.06±0.96, P = 0.012; LDL: ⊿2d: -0.26±0.74 vs. -0.027±0.64; P = 0.031; ⊿7d: -0.3±1.01 vs. 0.031±0.80, P = 0.059). Further comparison within the group demonstrated that blood lipid significantly decreased with time (Cholesterol: P = 0.020; LDL, P = 0.022) in urapidil group, while no significant change was found in nitroglycerin treated patients (Cholesterol: P = 0.886; LDL, P = 0.217). Therefore, urapidil may have the function of promoting lipid metabolism for patients with heart failure.

There was no difference in blood glucose between two groups of patients at different time points, and the blood glucose declined in the group over time. No significant difference of blood glucose level change was observed between urapidil-treated and nitroglycerin-treated groups (P>0.05) at different time points. Urapidil has no adverse effects on glucose metabolism.

*Comparison of medicines between patients of two groups (**Table 5**)*

The average dose concentrations of urapidil and nitroglycerin groups were 99.77±73.99 and 10.18±5.35 μg/min, respectively. The dose reduction in urapidil group

Table 5. Summarize of therapy and combined medicines between two groups

	Nitroglycerin (n = 115)	Urapidil (n = 107)	*P* value
Summary of medication			
Titration rate (μg/min)	10.18±5.35	99.77±73.99	<0.001*
Percentage of drug reaching target	68 (59.1%)	56 (52.3%)	0.308
Dose reduction rate	12 (10.4%)	23 (21.5%)	0.024*
Incidence rate of discontinuing study drug	2 (1.7%)	5 (4.7%)	0.211
Combination of medication			
Aspirin	80 (69.6%)	72 (67.3%)	0.715
Clopidogrel	55 (47.8%)	39 (36.4%)	0.086
ACEIs or ARBs	78 (67.8%)	75 (70.1%)	0.715
Statins	59 (51.3%)	53 (49.5%)	0.792
Diuretics	83 (72.2%)	72 (67.3%)	0.428
β-blockers	51 (44.3%)	50 (46.7%)	0.722

Data are presented as the mean ± standard deviation or n (%). *P<0.05. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 6. 7-day and 30-day MACE events between two groups

	Nitroglycerin (n = 115)	Urapidil (n = 107)	*P* values
7 days-MACE	5 (4.3%)	3 (2.8%)	0.789
Sudden cardiac death	0 (0)	0 (0)	
Non-fatal myocardial infarction	0 (0)	1 (0.9%)	0.480
Malignant arrhythmia	2 (1.7%)	0 (0)	0.498
Cardiac function deterioration	3 (2.6%)	2(1.9%)	0.711
30 days-MACE	17 (14.8%)	8 (7.5%)	0.085
Sudden cardiac death	1 (0.9%)	2 (1.9%)	0.950
Non-fatal myocardial infarction	0 (0)	1 (0.9%)	0.482
Malignant arrhythmia	2 (1.7%)	0 (0)	0.496
Rehospitalization or-/and- cardiac function deterioration	14 (12.2%)	5 (4.7%)	0.046*

Data are presented as n (%), *P<0.05.

was more common than that in nitroglycerin group (urapidil vs. nitroglycerin: 21.5% vs. 10.4%, P = 0.024). However, the incidence rate of discontinuing study medicines due to continuous hypotension (lower than 90/60 mmHg) between the two groups was similar (urapidil vs. nitroglycerin: 4.7% vs.1.7%, P = 0.221). The combined medication of the two groups was similar (P>0.05).

*Comparison of MACE between patients of two groups (**Table 6**)*

7 days and 30 days follow-up for MACE events showed that the incidence of adverse events in the two groups was similar (P>0.05). However, subgroup analysis for 30-day MACE showed that the readmission rate and-/or- deterioration of cardiac function in urapidil group was significantly lower than that of nitroglycerin group (4.7% vs. 12.2%, P = 0.046).

Discussion

Acute left heart failure is a common clinical emergency and severe disease that leads to sharp decrease of cardiac output and reflex excitability of adrenal medulla sympathetic nervous system, resulting in peripheral vascular contraction, increased cardiac after-load, and insufficient blood supply to tissue and organs, thus developing to cardiac shock and acute pulmonary edema, with high mortality. Elder patients are often complicated with multiple metabolic disorders, including diabetes, hyperlipidemia, metabolic syndrome and renal insufficiency, which further aggravate heart failure and complicate the condition by directly inhibit-

ing cardiac muscle, promoting blood vessel contraction and inflammation reaction [1, 2].

Urapidil is a derivative of phenylpiperazine and 4-aminouracil simultaneously working on both peripheral and central nervous systems. Urapidil works as a vasodilator that acts by blocking α-1 receptor of sympathetic postsynaptic membrane, dilating peripheral arteriovenous vessels, reducing cardiac pre-load and after-load so as to improve cardiac function. Meanwhile, the stimulation of central 5HT-1A-receptors reduces sympathetic tone and thus suppresses reflex tachycardia and increase renal blood flow. Therefore, urapidil decreases peripheral vascular resistance while remaining heart rate and peripheral renin activity [4, 6].

This study confirms the effects of urapidil and nitroglycerin is similar in quickly and continuously dilating blood vessels and relieving hemodynamic disorder of patients with heart failure. Compared with nitroglycerin, urapidil can better reduce cardiac load (ESV, EDV) and promote the increase of EF, which is consistent with results reported by Tebbe U et al [10] and Zink M et al [11], but in contrast with observation by Dorszewski et al [12]. Tebbe U et al (1988) [10], by using Swan-Ganz catheter, found that intravenous administration of Urapidil 25 mg for twice to patients with severe congestive heart failure significantly reduced SBP and mean blood pressure (MBP), as well as the peripheral circulation resistance, while increasing cardiac output (CO). Meanwhile, urapidil significantly promotes the drop of pulmonary artery pressure and pulmonary artery wedge pressure (PAWP) and reduces left ventricular pressure (end-diastolic volume, EDV), thus contributing to blood reflux and rapidly relieved symptoms of congestive heart failure, but has no significant influence on pulmonary arteriolar resistance. Zink M (2002) [11], by using (right ventricular ejection fraction) REF-Swan-Ganz catheter, found that intravenous administration of low dose of urapidil (10 or 20 mg) significantly reduced pulmonary vascular resistance and transpulmonary pressure of patients with end-stage congestive heart failure, and increased right heart ejection fraction (EF); its efficiency in reducing pulmonary vascular resistance was comparable, or even better than in reducing peripheral circulation resistance. On the contrary, Dorszewski et al (1997) [12] by treating patients with severe heart failure with urapidil (60-120 mg/d), no beneficial effects on hemodynamic parameters could be shown, and a trend toward increased mortality in the urapidil group was observed; Further investigation found that there were fewer patients enrolled in the group, cardiac function of urapidil treated group was significantly worse than control group, and 50% of the patients died from dilated cardiomyopathy. Considering that adverse effect of urapidil inducing arrhythmia or sudden death was not reported in previous literatures, the single report is not enough to prove that urapidil has the possibility of increasing the risk of death in patients with heart failure. Moreover, subgroup analysis of exercise tolerance of the patients survived showed that improvement of life was more significant than control group, which was consistent with our results that re-hospitalization rate or deterioration of cardiac function of urapidil-treated patients was lower than that of nitroglycerin-treated ones.

In the treatment of acute heart failure, compared with sodium nitroprusside [14] and nitroglycerin [15], urapidil caused no adverse impact on alveolar oxygen partial pressure, gas-exchange and ventilation-perfusion relationships, and intrapulmonary shunt fraction; and caused no risk of rapid resistance and poisoning metabolite; therefore, it benefits as continuous treatment during acute decompensation of heart failure patients. Compared with calcium channel blocker (CCB) [13], urapidil quickly controls the symptoms of pulmonary edema without causing significant negative effect of muscle contraction and negative inotropic action, and provides better promotion to pulmonary circulation than CCB. Moreover, urapidil also promotes reduction of plasminogen [16] and inhibits platelet aggregation [6]. Therefore, urapidil is a safe and effective vasodilator in the treatment of elder patients with heart failure.

75.2% patients enrolled in this study were complicated with coronary heart disease, and 50.9% were with heart failure after myocardial infarction. The 30 day-readmission rate and aggravation of heart failure of urapidil-treated group was significantly lower than that of nitroglycerin group, suggesting that urapidil provide therapeutic benefits to patients with ischemia and post-infarction heart failure, which is con-

sistent with conclusion reported by Gregorini et al [17-19] and Kozàkovà et al [20]. Gregorini et al [17-19] confirmed that urapidil (10 mg by intracoronary injection or 600 μg/kg by peripheral injection) significantly improved vasospasm of culprit lesion and non-culprit lesion, myocardial contractile dysfunction after ischemia; urapidil also increased the coronary flow reserve, coronary flow velocity and TIMI frame count. Similarly, Kozàkovà et al [20] also confirmed that intravenous administration (at 200 μg/kg/min) of urapidil significantly improved EF after receiving PCI for myocardial ischemia. Long-term oral administration may improve recovery of cardiac function after 3 months. The mechanism may be related to the fact that urapidil promotes coronary NO synthesis, reduces no-reflow risk of culprit vessel and slow-flow risk of non-culprit vessel after PCI procedure [21], increases diastolic time, improves epicardial myocardial perfusion [22], corrects the generation and consumption imbalance of systemic pulmonary endothelin-endothelin (ET)-ET1 and improves hemodynamic disorder [23].

In this study, the renal function of urapidil-treated group was significantly worse compared to nitroglycerin group, but the degree of elevation of serum creatinine and MACE follow-up outcome had no statistical difference; therefore, urapidil may provide additional benefits when treating severe heart failure patients complicated with renal insufficiency. This result is also supported by the conclusions reported by LAVRIJSSEN et al [24] and Semenova et al [25], in which they contribute such effect to reduction of the renal vascular resistance, improvement of renal perfusion, reduction of urinary retention [26], and relieving symptoms of heart failure.

Compared with nitroglycerin, urapidil can promote lipid metabolism in patients with heart failure without producing adverse effects on glucose metabolism, which was also supported by Flechtner-Mors et al [27] and Flechtner-Mors et al [28]. Considering the counteracting of urapidil to catecholamine (epinephrine and norepinephrine) induced fat catabolism, it directly improves the microcirculation of adipose tissue and inhibits the fat catabolism [27]. Urapidil also participates in reducing the high blood sugar induced by the release of catecholamine substances, increasing sensitivity to insulin, and promoting transformation of blood glucose [28]. Compared with ACEI and β-receptor blockers [29], urapidil provides unique advantages in patients with heart failure complicated with metabolic disorder.

Limitations

Urapidil Hydrochloride Injection, according to China version of indications for use, is intended to be used by patients with hypertension or complicated with hypertension (including hypertensive emergency or perioperative hypertension). Therefore, patients with SBP ranged between 110 to 140 mmHg (no hypertension history) were not included in multiple sites. Instead, we choose to keep waiting till enough patients with indications specified in the instructions were enrolled and then randomized. Therefore, patients in urapidil-treated groups were more severe in diseases with higher blood pressure and higher serum creatinine level after admission, as well as more severe disorder of blood lipid metabolism.

Conclusions

In summary, urapidil is a safe and effective vasodilator for elderly patients with acute left heart failure, which may provide additional benefits to elderly patients complicated with renal insufficiency and metabolic disorders due to its neutral or even positive effect on renal blood perfusion, blood lipid and blood glucose metabolism.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qi Hua, Department of Cardiology, Xuanwu Hospital, Capital Medical University, 45 Changchun Street, Xicheng, Beijing 100053, China. Tel: +86-13911469619; Fax: +86-10-83150948; E-mail: huaqimed@163.com

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