CRTER

Clinical Medicine

Effect of valsartan on the long-term prognosis of patients with coronary atherosclerotic heart disease following successful intervention therapy: Multicenter, double blind, randomized and controlled evaluation

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Abstract

BACKGROUND: Valsartan is an antagonist of angiotensin Ⅱ (Ang Ⅱ) receptor. Many researches have proved that it can protect heart tissue. Val-PREST suggests that valsartan with a long-term administration can decrease restenosis rate in stent; however, effect of valsartan on restenosis rate of Chinese population is still unclear presently.

OBJECTIVE: To evaluate the effect of oral valsartan for 6 months on patients with coronary heart disease (CHD) who undertook successful intervention therapy.

DESIGN: Multicenter, double blind, randomized, and controlled evaluation and prospective design.

SETTING: Beijing Friendship Hospital Affiliated to Capital Medical University; Beijing Anzhen Hospital Affiliated to Capital Medical University; Peking Union Hospital; People's Hospital of Peking University; Beijing Tongren Hospital Affiliated to Capital Medical University; Beijing Shijingshan Hospital; Beijing Fuxing Hospital Affiliated to Capital Medical University; Beijing Chuiyangliu Hospital.

PARTICIPANTS: Eight three-grade A hospitals in Beijing participated in the study. Since December 2002 to October 2003, a total of 200 patients who underwent bare mental stent implantation were consented, but 196 patients were recruited in the end. All 196 patients were randomized into valsartan group (100 cases) and control group (96 cases).

METHODS: Basic medicines in the two group included aspirin, clopidogrel, nitrides, statins, β-receptor antagonists, calcium channel antagonists, *etc*. Additionally, Patients in valsartan group were also given valsartan (Beijing Nuohua Pharmaceutical Co. Ltd., batch number: SD 34004) in a dosage of 80 mg a day. Both groups were followed-up once a month for total 6 months.

MAIN OUTCOME MEASURES: ① Major adverse cardiac events within 6 months on clinics (death, non-fatal myocardial infarction, hospitalisation once more due to recurrent myocardial ischemia, and target vessel revascularization); ② Results of duplicated coronary angiography or exercise treadmill test (ETT) of partial patients within 6 months.

RESULTS: ① Two patients (2%) in valsartan group were excluded in this study because of intolerance, so 194 patients were involved in the final analysis. ② No significant differences of baseline characteristics in terms of lesion type, the number of diseased vessels and the cardiac function were found between the two groups ($P < 0.05$). ③ During the period of 6-month follow-up, one case died in control group. One acute myocardial infarction occurred in each group, whilst one case undertook target vessel revascularization in valsartan group. It was found that the proportion of recurrent cardiac events was lower in valsartan group than that in control group (11.2% *vs.* 15.6%). However, this difference did not reach the statistic significance. ④ During the period of 6-month duplicated contrast examination, one case had restenosis of in-stent in valsartan group. ⑤ The positive rate of exercise treadmill test (ETT) was lower in valsartan group (25.7%) than that in control group (36.4%), but there was no statistic difference.

CONCLUSION: Six-month oral valsartan on patients with coronary heart disease who undertook successful intervention therapy can decrease the trend of recurrent cardiac events and positive rate of ETT.

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INTRODUCTION

Pharmacological interventions that influence the renin-angiotensin system (RAS) by inhibiting the angiotensin-converting enzyme (ACE) or the angiotensin Ⅱ (Ang Ⅱ) type 1 receptor (AT Ⅱ 1R) have demonstrated sustained efficacy in reducing the incidence of cardiovascular events and, consequently, cardiac mortality in several clinical trials by reducing blood pressure and having cardio- and vasculoprotective effects. Hence, it has been hypothesized that RAS inhibitors might also reduce the recurrence of ischemic events after myocardial revascularization procedures, such as percutaneous coronary interventions (PCI). However, present data regarding the progression of CAD, in terms of restenosis or reocclusion rate after myocardial revascularization are inconsistent. Quite several studies that evaluated a possible anti-atherosclerotic effect of ACE inhibitors have generally been negatively reported. Conversely, a single, randomized trial demonstrated that the selective AT1R antagonist valsartan significantly reduced in-stent restenosis after PCI. However, the result needs to be confirmed in a large multicenter trial obviously. The aim of the present study was to examine the effect of valsartan on patients with coronary heart disease (CHD) after successful revascularization in Chinese population.

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SUBJECTS AND METHODS

Subjects

Eight three-grade A hospitals in Beijing participated in the study, including Beijing Friendship Hospital Affiliated to Capital Medical University; Beijing Anzhen Hospital Affiliated to Capital Medical University; Beijing Union Hospital; People's Hospital of Peking University; Beijing Tongren Hospital Affiliated to Capital Medical University; Beijing Shijingshan Hospital; Beijing Fuxing Hospital Affiliated to Capital Medical University; Beijing Chuiyangliu Hospital. Since December 2002 to October 2003, a total of 200 patients who underwent bare mental stent implantation were consented, but 196 patients were recruited in the end, because four of them changed their mind. It was found that there was not significant difference in terms of the basic characteristics and clinical factors between the participation groups. Inclusion criteria: All patients were aged from 18 to 75 years, with documentary diagnosis of CHD by clinical coronary angiography, and having undergone successful bare mental stent implantation. Exclusion criteria: Those with severe hepatic or renal dysfunction including dialysis (serum creatinine > 256 μmol/L or 3 mg/dl) or patients who had ever taken Ang Ⅱ receptor antagonists, or those who were diagnosed acute coronary syndrome (ACS) and accepted primary or rescued PCI were excluded. All 196 patients were randomized into valsartan group (100 cases), who accepted six-month therapy of orally administration with valsartan (Beijing Nuohua Pharmaceutical Co. Ltd., batch number: SD 34004) in a dosage of 80 mg a day, and into control group (96 cases), who underwent the usual medical therapy.

Methods

There were no significant differences in other medical treatments between the valsartan and control groups regarding the categories and the dosages in drug therapy, which included aspirin, clopidogrel, nitrides, statins, β-receptor antagonists, calcium channel antagonists and angiotensin-converting enzyme (ACE) inhibitors. Both groups were followed-up once a month for total 6 month, with strict recording for any clinical adverse cardiovascular events including death, non-lethal myocardial infarction, reoccurred myocardial ischemia, and recurrent revascularization.

Statistical analysis: All data were analyzed by SPSS 11.0 soft ware by comparing the valsartan and control group with student's *t* test for the continuous variables and Chi-square test for categorical variables. Data were expressed as Mean ± SD. Statistic significance was assessed in a level of $P < 0.05$.

RESULTS

Quantitative analysis of the participants

All 194 patients were involved in the final analysis. One patient was excluded for severe hypotension and another one for severe gastrointestinal symptoms during the following-up in valsartan group.

Comparisons of baselines in the two groups

There were no significant differences between the valsartan and control groups regarding the assessment of blood lipid indices, white blood cells, C-reaction protein, renal function, hepatic function and cardiac function (Tables 1 and 2).

Flow chart (Figure 1)

Angiographic results and prognosis

It was not found that there were any significant differences in terms of lesion types and the number of diseased vessels between the two groups. Successful PCI rate in the two groups was 100% (Table 3).

There were no significant differences in MACE (major adverse cardiac events) between the two groups though it seemed that MACE were more seen in control group than valsartan group. One patient died of AMI in control group and no patient died in valsartan group during six-month follow-up. The incidence of reoccurred myocardial ischemia in valsartan group was lower than control group, but the difference did not reach the statistical significance either, while one revascularization of the target vessel was completed in the valsartan group. Repeated angiography at 6th month in one patient of valsartan group implied in-stent restenosis. Positive rate of ETT was obviously less in the valsartan group than in the control group, but with no statistical significance yet (Table 4).

Table 1 Comparisons of clinical characteristics in the two groups

Characteristics	Valsartan (n=98)	Placebo (n=96)	t/χ^2	P
Age (yr)	61.8±16.1	61.6±11.6	t=0.10	> 0.05
Gender (M/F%)	76.8/23.2	70.8/29.2	χ^2=0.81	> 0.05
Height (cm)	166.6±14.1	165.5±9.8	χ^2=0.63	> 0.05
Weight (kg)	71.3±10.2	73.4±11.3	t=1.36	> 0.05
SBP (mm Hg)	132.2±26.5	130.5±23.0	t=0.48	> 0.05
DBP (mm Hg)	79.3±14.1	78.2±13.3	t=0.56	> 0.05
Smoking (n/%)	62/63.3	51/53.2	χ^2=2.05	> 0.05
Hypertension (n/%)	62/63.3	64/66.7	χ^2=0.24	> 0.05
Diabetes (n/%)	18/18.4	21/21.9	χ^2=0.37	> 0.05
Hyperlipidemia (n/%)	37/37.8	44/45.8	χ^2=1.30	> 0.05
Family History (n/%)	33/33.7	42/43.8	χ^2=2.07	> 0.05
Myocardial Infarction (n/%)	13/13.3	10/10.4	χ^2=0.37	> 0.05
PCI (n/%)	4/4.1	3/3.1	χ^2=0.12	> 0.05
Stroke (n/%)	9/9.2	8/8.3	χ^2=0.04	> 0.05
Diagnosis				
UAP/NSTEMI (n/%)	63/64.3	58/60.4	χ^2=0.30	> 0.05
AMI (n/%)	32/32.7	32/33.3	χ^2=0.01	> 0.05
SAP (n/%)	3/3.1	6/6.3	χ^2=1.11	> 0.05
Cardiac Function (NYHA)				
Grade 1(n/%)	53/53.1	61/63.5	χ^2=1.79	> 0.05
Grade 2 (n/%)	41/41.8	29/30.2	χ^2=2.84	> 0.05
Grade 3 (n/%)	4/5.3	6/6.3	χ^2=0.46	> 0.05

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PCI: Percutaneous coronary intervention; UAP: Unstable angina pectoris; NSTEMI: Non-ST elevation myocardial infarction; AMI: Acute myocardial infarction; SAP: Stable angina pectoris; NS: Non-significance

Table 2 Comparisons of clinical results in the two groups ($\bar{x}\pm s$)

Biochemistry indices	Valsartan (n=98)	Placebo (n=96)	t	P
TC (mmol/L)	4.60±0.98	4.78±1.22	1.09	> 0.05
TG (mmol/L)	4.03±2.57	4.12±3.04	0.22	> 0.05
LDL (mmol/L)	2.83±0.76	2.88±0.91	0.43	> 0.05
HDL (mmol/L)	1.04±0.23	1.03±0.24	0.15	> 0.05
ApoA (g/L)	0.26±0.48	0.15.1±0.39	1.74	> 0.05
ApoB (g/L)	0.16.0±0.29	0.15.2±0.40	0.16	> 0.05
HsCRP (mg/L)	63±53	50±48	1.38	> 0.05
WBC ($\times10^9L^{-1}$)	79±25	76±23	0.87	> 0.05
Neu (%)	67.3±16.0	70.1±10.2	1.45	> 0.05
Lym (%)	28.2±14.5	25.6±9.1	1.50	> 0.05
Cr (μmol/L)	88.4±17.7	106.1±106.1	1.61	> 0.05
BUN (mmol/L)	4.57±2.14	4.82±2.0	0.84	> 0.05
GOT(v/L)	31±22.5	41±59.8	1.53	> 0.05
TnT (ng/L)	5±5	4±5	1.40	> 0.05

TC: Total cholesterol; TG: Triglycerin; LDL: Low density lipoprotein; HDL: High density lipoprotein

Adverse events and side effects

Hypotension observed on one patient in valsartan group lasted for 3 days, and the symptom was recovered after withdrawal administration. Gastrointestinal symptoms, such as nausea and emesis, were observed on the other patient and lasted for 5 days. the symptom was recovered after withdrawal administration.

DISCUSSION

Valsartan is a non-peptide Ang Ⅱ receptor antagonist, which is highly selective, specific and high-affinity to AT1R without blocking the AT2R. It can competitively block the Ang Ⅱ receptor without activating it and inhibit Ang Ⅱ to induce adenosine glomerule to release aldosterone.

Neuroendocrine system participates in each slides of pathophysio-

logical progress of cardiovascular events. Activation of RAAS results in vascular endothelial dysfunction, endothelial cell propagation and metastasis, accelerating oxidation of LDL, facilitating artery atherosclerosis. Disorder of fibrolysis system is prone to induce thrombosis and causes accumulation of myocardial matrix which might aggravate heart failure. Ang II can increase expressions of endothelium and smooth muscle cell PAI-1 through AT1 receptor [1]. Valsartan can increase activity of t-PA, decrease activity of PAI-1, and improve equilibration of fibrolysis system [2]. Ang Ⅱ can also induce early platelet activation and increase PAI-1 excretion[3]. Leszek Kalinowski *et al* [4] prove that AT1 receptor antagonist including valsartan can activate NOS, increase release of NO and inhibit platelet aggregation.

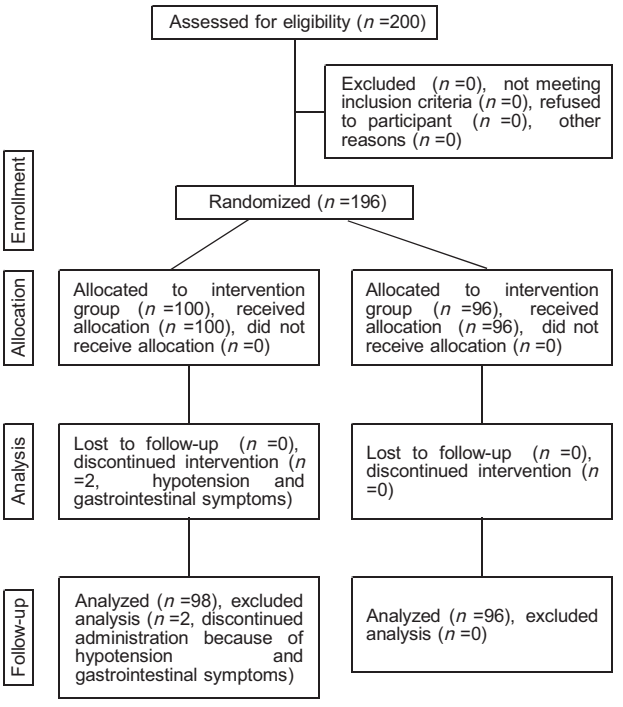

Figure 1 Flow chart of a randomized trial

Table 3 Angiographic results in both groups (%)

Interventional data	Valsartan (*n*=98)	Placebo (*n*=96)	χ^2	*P*
Lesion Type				
a/b1	43.9	42.7	0.02	> 0.05
b2	31.6	33.3	0.06	> 0.05
c	24.5	24.0	0.00	> 0.05
Vessel				
Single	50.0	52.1	0.08	> 0.05
Dual	32.3	30.2	0.13	> 0.05
Triple	17.6	16.7	0.01	> 0.05
PCI	100	100	0.00	> 0.05

PCI: Percutaneous coronary intervention

It has been investigated that Ang II could prompt the expression of ET mRNA and instigate the synthesis of functional ET in humane vascular smooth muscle cell[5-7]. At the same time, ET could also improve synthesis and releasing of Ang II in endothelial cells and VSMCs, which is supposed to be a positive feedback to accelerate the hyperplasia of VSMCs. Some studies have concluded that[2] valsartan could inhibit the decrease of endothelium-dependant diastolic function of aortic circle in hypercholesterolemia mouse. In China, Tong *et al* [8] explored that the changes of ET, PCNA, TXB2 and 6-keto-PGF1α and confirmed that valsartan could inhibit propagation of the endothelium after vascular injury. Since AngII could stimulate metastasis and hyperplasia of coronary artery smooth muscle, hence valsartan may inhibit coronary artery smooth muscle metastasis and hyperplasia, therefore regulate the pace of coronary atherosclerosis simply by blocking the AngII-AT1 receptor [9]. Oxide free radicals (OFR) have been found to induce the injury of endothelial function[10]. Ang Ⅱ combining with AT1 receptor prompts OFR by NADH/NADPH oxygenase. Researches approved that long-term administration of valsartan protected endothelial function by inhibiting OFR in post-myocardial infarction[11].

Table 4 Prognostic results in both groups (*n*/%)

Prognosis	Valsartan (*n*=98)	Placebo (*n*=96)	χ^2	*P*
MACE	12/12.2	17/17.6	1.13	> 0.05
AMI	1/1	1/1	0.00	> 0.05
Death	0	1/1	1.02	> 0.05
Recurrent myocardial ischemia	11/11.2	15/15.6	0.80	> 0.05
TVR	1	0	0.98	> 0.05
Repeated CAGs at the 6th month In-stent restenosis	14 1/1	5 0	0.98	> 0.05
ETT at the 6th month	35	22		
Positive	9/25.7	8/36.4	0.73	> 0.05
Negative	26/74.3	14/63.6	0.73	> 0.05

MACE: Major adverse cardiac events; AMI: Acute myocardial infarction; CAG: Coronary angiography; ETT: Exercise treadmill test; TVR: Target vascular revascularization

Val-PREST study [12] is the first randomized, placebo-controlled study to evaluate the effect of an angiotensin receptor antagonist valsartan on in-stent restenosis in a moderate number of patients. The results indicated that, after 6-month treatment, valsartan could significantly reduce the incidence of restenosis compared to the placebo [19.2% (19/99) *vs.* 38.6% (39/101), $P < 0.005$]. It was also found that compared to the control group, in which 28.7% (29/101) of the patients received a recurrent revascularization, while only 12.1% (12/99, $P < 0.005$) of patients were recorded of this performance in valsartan group. It was discussed that the potential underline mechanisms that valsartan can significantly reduce the restenosis after a revascularization in CAD could be: ① Valsartan can inhibit the oxygenation of LDL and therefore slow down the pace of atherosclerosis [13]; ② It reduce the releasing of free radicals and vascular contraction[14,15]; ③ Schieffer *et al*[16] affirmed that valsartan has anti-inflammation effects on substances during coronary rotating athectomy; ④ Valsartan might probably inhibit the hyperplasia of vascular smooth muscle by blocking the co-operating effect of PDGF and EGF in the similar way of candesartan does[17,18].

The results in the present study indicated that valsartan did reduce cardiovascular events in the Chinese CAD patients group who underwent a selective revascularization. Reoccurring ischemia rate in valsartan group (11.2%) was slightly lower than the control group (15.6%). The rate of positive result of ETT in valsartan group was also lower than control group (25.7% *vs.* 36.4%), but there was no statistical significance between them. The explanation for this result might be: ① The sample size may not be big enough to reach the significance statistically in between the two groups. ② Since ACEIs were used in more than 80% of the patients in the control group, while β-blockers and calcium antagonists were used in those patients who did not take ACEIs, it was very difficult to find out the advantages of valsartan. ③ The patients with a/b1 type lesions were not excluded during recruit, among whom the incidence of occurring of any cardiovascular events was reported to be very low after a successful PCI. Besides, one of the other major limitations of the present study is that since the target index in observation was based only on clinical events, *i.e.* mortality, cardiac recurrence and revascularization, and due to the small sample size, there was also small incidence of any positive results in ETT and angiographic during the period of following-up, therefore it failed to elucidate the significant efficacy of valsartan on reducing the in-stent restenosis.

Presently, a lot of researches have proved that not only can valsartan decrease blood pressure, but can resist oxidation and inflammation, regulate proliferation, migration and apoptosis through changing molecular signal conduction, delay myocardial reconstruction, protect cardiac function and vascular endothelial function [19-21], and prevent

and cure PCI restenosis[22]. This study has further proved that valsartan could relieve cardio-vascular events after stent implantation.

Nevertheless, the present data have illustrated some effects of valsartan on reducing the in-stent restenosis after revascularization in Chinese CAD patients, though not significantly in a statistical level. Further studies with larger sample size and better controlling with clinical drug using, in a multicenter set, in terms of randomized trial might be prospected, along with those explorations to uncover the underline mechanisms regarding to valsartan's reducing the in-stent restenosis in patients after revascularization.

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缬沙坦对冠状动脉粥样硬化性心脏病患者介入治疗后长期预后的影响:多中心双盲评估的随机对照研究★

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摘要

背景:缬沙坦是一血管紧张素Ⅱ受体拮抗剂,已有相当多的试验证实它对于心脏的保护作用。Val-PREST研究证实长期口服缬沙坦可使支架内的再狭窄率显著降低,但目前缺乏缬沙坦对中国人支架植入术后再狭窄率影响的研究报道。

目的:评价成功介入治疗后的冠状动脉粥样硬化心脏病(简称冠心病)患者口服6个月缬沙坦对临床事件的影响。

设计:多中心、随机对照、双盲法评估,前瞻性设计。

单位:首都医科大学附属北京友谊医院、首都医科大学附属北京安贞医院、北京协和医院、北京大学人民医院、首都医科大学附属北京同仁医院、北京市石景山医院、首都医科大学附属北京复兴医院、北京市垂杨柳医院。

对象:在北京8家3级甲等医院入选200例金属裸支架介入治疗成功后的冠心病患者,按照统一的随机号随机分为缬沙坦组和对照组各100例,入选工作2002-12/2003-10完成。实际入选病例数196例(缬沙坦组100例,对照组96例)。

干预措施:两组基础用药相同(包括阿司匹林、氯吡格雷、硝酸酯类药物、他汀类药物、β-阻滞剂或钙离子拮抗剂等),缬沙坦组在此基础上加用缬沙坦80 mg(北京诺华制药有限公司,批号:SD 34004),1次/d口服。所有患者随访6个月。

主要观察指标:①6个月临床心血管不良事件(死亡、非致命性心肌梗死、复发心肌缺血、靶血管再次血运重建)。②6个月时部分患者完成重复冠脉造影检查或运动试验,观察结果。

结果:①缬沙坦组有2例(2%)因药物耐受不良在随访过程中退出试验,共有194例完成随访。②2组患者基础情况没有差异,病变类型、心功能及病变血管支数均没有统计学差异($P > 0.05$)。③6个月随访时,对照组死亡1例,两组各有1例急性心肌梗死发生,缬沙坦组1例进行了靶血管重建,复发心肌缺血事件缬沙坦组略低于对照组(11.2% 比 15.6%),但未达到统计学差异。④6个月重复血管造影在缬沙坦组有1例发生支架内再狭窄。⑤6个月复查运动试验缬沙坦组阳性(25.7%)的比例低于对照组(36.4%),但未达到统计学差异。

结论:成功介入治疗后的冠心病患者口服6个月缬沙坦有降低复发心肌缺血事件和运动试验阳性率的趋势。

关键词:缬沙坦;冠心病;运动试验

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