

Efficacy and Safety of Intravenous Nicorandil on blood pressure in patients with coronary heart disease Corresponding author: Yan He, Email :heyang20200418@126.com

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Abstract

Aims The study was to investigate the effects of Intravenous Nicorandil on blood pressure and drug safety in patients with coronary heart disease. **Methods** In order to evaluate the blood pressure lowering effects and safety of Intravenous Nicorandil, we recruited 43 inpatients with unstable angina to intravenously pump Nicorandil, and the pumping speeds (2mg/h, 4mg/h and 6mg/h, respectively) were adjusted according to the patient's blood pressure. After treatment, the effects of Intravenous Nicorandil on blood pressure and drug safety were observed. **Results** After treatment, the average reduction in SBP was 22.86 ± 19.83 mmHg, and the average reduction in DBP was 9.80 ± 18.58 mmHg. And Nicorandil could decrease patients blood pressure in a concentration-dependent manner. During the following-up, no serious adverse events were observed. **Conclusion** Intravenous Nicorandil could significantly reduce systolic and diastolic blood pressure in patients without affecting heart rate, and it reduced in depending on concentrations, suggesting that Intravenous Nicorandil may be a new intravenous antihypertensive drug in future clinical application.

Efficacy and Safety of Intravenous Nicorandil on blood pressure in patients with coronary heart disease

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Results

After treatment, the average reduction in SBP was 22.86 ± 19.83 mmHg, and the average reduction in DBP was 9.80 ± 18.58 mmHg. And Nicorandil could decrease patients blood pressure in a concentration-dependent manner. During the following-up, no serious adverse events were observed.

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Keywords

Intravenous Nicorandil; blood pressure

1. Introduction

Angina is one of the common clinical diseases. It is caused by insufficient oxygen supply to the myocardium due to coronary artery stenosis caused by coronary sclerosis or coronary artery spasm. Therefore, reducing myocardial oxygen consumption and increases coronary blood flow and then restores the balance between supply and demand of ischemic myocardial oxygen, at the same time, the prevention and treatment of atherosclerosis also are the fundamentals of angina treatment. Nicorandil is a well-known antianginal agent, which has been recommended as one of the second-line treatments for chronic stable angina as justified by the European guidelines¹. It shows an efficacy equivalent to that of classic antianginal agents. Nicorandil has also been applied clinically in various cardiovascular diseases such as variant or unstable angina and reperfusion-induced damage following coronary angioplasty or thrombolysis^{2,3}. The mechanisms have been involved in the protective effects of Nicorandil in angina through either opening of adenosine triphosphate-sensitive potassium (K-ATP) channel or donation of nitric oxide (NO)^{4,5}.

Coronary heart disease patients are usually accompanied by hypertension. When experiencing angina pectoris, the patients often had an increase in blood pressure. Clinically, when this happened, intravenous isosorbide mononitrate and nitroglycerin are used to prevent angina, and the same time to control blood pressure. We all know that isosorbide mononitrate and nitroglycerin have anti-angina pectoris and affect blood pressure related to its release of nitric oxide factor⁵. Similarly, Nicorandil administration also increases the level of NO through reaction of its nitrate group with sulfhydryl group in cells of vascular smooth muscle⁴. Therefore, we speculate that Intravenous Nicorandil may also affect blood pressure. The effect of Intravenous Nicorandil on angina is well established, but few reports demonstrated that Nicorandil may cause severe vasodilation and fall in blood pressure, the impact of Intravenous Nicorandil on blood pressure has not been investigated till now.

Therefore, the aim of the study was to investigate the effects of Intravenous Nicorandil on blood pressure and drug safety in patients with coronary heart disease.

2. Methods

2.1 Patients

This study screened 43 inpatients with unstable angina from the Department of Geriatric Cardiology, the First Affiliated Hospital of Guangxi Medical University from May 1, 2019 to December 1, 2019, The age of included patients was between 39 and 64 years, with a mean age of 51.54 ± 12.70 years.

2.2 Methods

After admission, patients with unstable angina were given aspirin + clopidogrel or ticagrelor, statins, low-molecular-weight heparins, and the use of ACEI and receptor blockers to prevent secondary coronary heart disease. Based on this treatment, Nicorandil was intravenously pumped, and the pumping speeds (2mg/h, 4mg/h and 6mg/h, respectively) were adjusted according to the patient's blood pressure. We adjusted Nicorandil speed in half an hour, and continuously pumped total of 36mg before stopping the drug. During the treatment, observe the changes in blood pressure and heart rate of the patients before and after

treatment, and observe whether the effect of Intravenous Nicorandil on the blood pressure of the patients is concentration-dependent, and monitor the adverse reactions during the medication.

2.3 Statistical analysis

The SPSS 21.0 statistical software package was used for all the statistical analysis, Continuous variables were expressed as mean \pm standard deviation(SD) and categorical variables were presented as frequent count and percentages. The comparison of inter-group analysis of BP levels and HR was performed by unpaired two-tailed t-test. Two-tailed $P < 0.05$ was treated as statistically significant.

3. Results

3.1 Changes in blood pressure and heart rate before and after treatment

A total of 43 patients were enrolled in this study. After Intravenous Nicorandil treatment, there was induced a significant decrease in levels of SBP and DBP ($p < 0.01$) (Table 1). After treatment, the average reduction in SBP was 22.86 ± 19.83 mmHg, and the average reduction in DBP was 9.80 ± 18.58 mmHg. In addition, we also compared changes in heart rate before and after treatment (Table 1), and there was no significant statistical difference ($p > 0.05$).

3.2 Nicorandil decreases patient blood pressure in a concentration-dependent manner

In this study, the intravenous pumping rate of Nicorandil was adjusted according to the patient's blood pressure levels, and the effect of different concentrations of Nicorandil on the patient's SBP and DBP was observed (Table 2). It was found that the systolic blood pressure of the patients can be significantly reduced compared with the baseline blood pressure when the pumping rate of Nicorandil at 4 mg/h and 6 mg/h, respectively ($p < 0.01$) (Figure 1). And the reduction in systolic blood pressure was 18.00 ± 18.01 , 27.04 ± 17.25 respectively. And compared with the baseline DBP, the levels of DBP decreased significantly when the pumping rate of Nicorandil were 4 mg/h and 6 mg/h ($p < 0.01$) (Figure 2). And the reduction in DBP was 8.71 ± 9.01 and 15.17 ± 12.93 , respectively. But when the pumping speed is 2 mg/h, there is no significant statistical changes compared with the baseline SBP and DBP. ($p > 0.05$) (Figure 1 and Figure 2). These showed that Nicorandil could decrease patients blood pressure in a concentration-dependent manner.

3. Safety profile

During the entire observation process, one patient experienced dizziness, two patients experienced headaches, one patient experienced blushing, one patient experienced orthostatic hypotension. All of the above patients were discontinued due to the adverse reactions described above. But, the above symptoms improved after the drug was stopped.

4. Discussion

Nicorandil is a safe, well-known antianginal agent that has been approved as a long-term therapy for angina in Japan and Europe⁶. The Japanese Coronary Artery Disease (CAD) and the Impact of Nicorandil in Angina studies have revealed a beneficial impact for Nicorandil on mortality and morbidity in patients with CAD^{7,8}. The use of Nicorandil has been recommended by the European Society of Cardiology as one of the second-line treatments for chronic stable angina¹. Overall, comparative clinical trials have shown an equivalent efficacy of Nicorandil in improving effort angina and ischemic symptoms compared to β blockers and calcium antagonists with minimal hemodynamic disturbance⁹. Interestingly, a meta-analysis from 17 clinical trials has demonstrated that Nicorandil treatment ameliorated left ventricular ejection fraction and microvascular function when used in patients with acute myocardial infarction (AMI) in conjugation with coronary reperfusion therapy¹⁰. Long-term therapy of Nicorandil also showed beneficial effects on left ventricular remodeling and sympathetic nerve activity of myocardium in patients with AMI when used after reperfusion therapy¹¹. In addition, Nicorandil treatment when used as adjunctive to coronary angioplasty was accompanied by better clinical and functional outcomes in patients with anterior AMI compared to angioplasty alone. This was mainly attributed to a decrease in myocardial injury and improvement in microvascular function and rate of no-reflow¹². Another study revealed that intravenous nicorandil reduced

QT dispersion and ventricular fibrillation in patients after successful coronary angioplasty¹³. But few studies had reported that Intravenous Nicorandil intake was associated with significant drop in blood pressure. While, in our research, we found Intravenous Nicorandil could significantly reduce systolic and diastolic blood pressure in patients without affecting heart rate, and it reduced in depending on concentrations. Other than that, several reports demonstrated that Nicorandil may cause severe vasodilation and fall in blood pressure when used preoperatively before coronary artery bypass graft¹⁴. So we can speculate that Nicorandil, like nitroglycerin, may relieve angina and affect blood pressure at the same time.

The vasodilating effect of Nicorandil is related to the effect of opening the ATP-sensitive K channel, as well as to the effect of increasing production of cGMP⁴. ATP-sensitive K channel which not only exists in coronary endothelium, but also in peripheral vascular smooth muscle cells¹⁵. Probably, Nicorandil may activate and open ATP-sensitive K channel of the cell membrane of vascular smooth muscle cells, thus promote the potassium efflux, which leads to vascular smooth muscle cell membrane hyperpolarization. Furthermore, T-type voltage-dependent calcium channel is closed, reducing intracellular calcium concentration and inhibiting vascular smooth muscle contraction, therefore affects blood pressure¹⁶. Meanwhile, Nicorandil can activate guanine cyclase¹⁷, which could increase cGMP in smooth muscle and other tissues, resulting in dephosphorylation of myosin light chain, regulating vascular smooth muscle contraction, peripheral vein dilatation, blood retention in the peripheral, decreasing re-turned blood volume and left ventricular end diastolic pressure (LVEDP), dilating the artery reduces peripheral resistance. Arteriovenous dilation reduces myocardial oxygen consumption and relieves angina, so it may also decrease blood pressure.

The major adverse reactions of this drug were headache, hepatic function disorder, thrombocytopenia, increased total bilirubin, increased LDH, anemia, and increased γ -GTP^{18,19}. In our trial, patients also experienced dizziness, headache, blushing and other discomforts, but the difference is that one patient developed orthostatic hypotension, and its possible mechanism may be related to the rapid infusion of Nicorandil which resulted in a rapid drop in blood pressure.

In our trials, we found that Intravenous Nicorandil had a significant effect in blood pressure lowering and was also safe. Because the sample size of this study is relatively small, and most of our patients are elderly, they may not represent the entire population, so a larger and more comprehensive clinical trial is needed. As the trial progresses, Intravenous Nicorandil may be used, like nitroglycerin, to relieve angina, and the same time, to lower blood pressure. However, we should pay more attention to the pumping speed of nicorandil in the process of using Nicorandil, especially to the elderly, and we must try our best to avoid the risk of orthostatic hypotension.

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