ORIGINAL RESEARCH

Efficacy and Safety of Nicorandil in the Treatment of Stable Angina Pectoris

Xuan Wang, MM; Haojing Chen, MM

ABSTRACT

Background • Stable angina pectoris (SAP) is an ischemic heart disease caused by coronary artery stenosis, which usually occurs during physical activity or emotional excitement. For this type of angina pectoris, reducing the oxygen demand of the heart and increasing the coronary blood flow are the key goals of treatment.

Objective • To analyze nicorandil's application effect and adverse reactions in patients with SAP.

Methods • Sixty patients with stable angina pectoris admitted to our hospital from December 2020 to May 2022 were randomly selected and included in this study. They were divided into nicorandil group (n=30) and conventional group (n=30). The clinical efficacy, duration of chest pain, number of heart attacks per week, cardiac function indexes, improvement of exercise tolerance, occurrence of adverse reactions, and Seattle Angina Scale (SAQ) score were observed.

Results • The effective rate of nicorandil group was 93.33%, which was much higher than that of conventional group (73.33%, $P < .05$). The results showed that the nicorandil group was significantly better than the conventional group in clinical efficacy, duration of chest pain, number of attacks per week, cardiac function index, improvement of exercise tolerance, occurrence of adverse reactions and SAQ score ($P < .05$).

Conclusions • Nicorandil can improve the clinical symptoms of SAP patients, significantly reduce the duration and frequency of chest pain attacks, and enhance cardiac function indicators. It can be used as an effective drug choice to reduce the frequency and intensity of angina pectoris attacks and is worthy of wide clinical application. (*Altern Ther Health Med.* 2024;30(5):130-135)

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INTRODUCTION

Angina pectoris is divided into Stable angina pectoris (SAP) and unstable angina pectoris. The most common type of angina pectoris is SAP, also known as stable labor angina pectoris. SAP is a condition of insufficient blood supply to the heart caused by coronary artery stenosis. Patients with SAP may also have angina pectoris symptoms at rest or during mild activity, and these symptoms are relatively stable for a period of time. With the development of the disease, the frequency and duration of angina pectoris may increase, which seriously affects the quality of life of patients. Usually, the symptoms of this type of angina pectoris are relatively fixed and predictabl and related to specific activities or situations. Symptoms usually occur at a relatively fixed level, and patients can be relieved by resting or using nitrates. Unstable angina pectoris, on the other hand, is unpredictable and serious, which may be a precursor of serious cardiovascular events. Unstable angina pectoris usually indicates that coronary insufficiency has worsened, which may be a precursor of acute coronary syndrome and needs urgent medical attention.

It is a clinical syndrome of acute and transient myocardial ischemia and hypoxia caused by the increase of myocardial load based on severe fixed coronary artery stenosis. Emotional agitation, physical labor, and climate change may all lead to the occurrence of this disease.[1,2] Its clinical manifestations are mainly parochial and transient retrosternal squeezing pain or suffrage, seriously affecting patients' daily lives and exercise. Drug therapy is the golden solution for SAP treatment.[3] At present, the comprehensive application of antiplatelet drugs, cholesterol-lowering drugs, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-II receptor antagonists (ARB), β adrenergic receptor blockers (β-blockers), nitrates, calcium channel blockers, and other drugs is often used to prevent the occurrence of cardiovascular events and angina

pectoris in SAP patients Symptom relief. However, the expected results are not completely ideal, there is still room for improvement.[4] Nicodil is a potassium channel opening drug that can theoretically improve coronary blood flow and myocardial energy metabolism, but few relevant studies exist.[5] At present, although there are many treatment strategies to choose from, there are still many patients who cannot get effective treatment. This is mainly because there are some challenges and limitations in the existing drug therapy, such as the reduction of long-term curative effect, side effects and the different responses of patients to drugs. Therefore, it is necessary to explore new treatment methods to improve the therapeutic effect and safety of SAP. Nicorandil is a unique drug, which has the dual action mechanism of nitrate and potassium channel opener, and may provide new possibilities for the treatment of SAP.

Nicardipine reduces the influx of calcium ions by blocking calcium channels on cell membranes, especially L-type calcium channels in heart and smooth muscle cells. This leads to relaxation of vascular smooth muscle and inhibition of the heart, thus lowering blood pressure and reducing the burden on the heart. The purpose of this study is to evaluate the clinical efficacy and safety of nicorandil in the treatment of SAP patients. Based on this, nicodil was applied in SAP patients in this study to analyze patients' clinical efficacy and adverse reactions after medication. Relevant reports are as follows.

PATIENTS AND METHODS

Baseline Data

A total of 60 patients with SAP admitted to our hospital from December 2020 to May 2022 were included in the study and divided into nicorandil group and conventional group according to the computer number table method, with 30 cases in each group. The specific method is to use a computer program to generate a series of random numbers, which represent potential patient numbers. Each number has an equal probability of being assigned to the nicorandil group or the conventional group.

The age of patients in nicorandil group was 71.10±6.01 years old, and that in routine group was 72.80±6.18 years old. There were 17 males and 13 females in nicorandil group. There were 16 males and 14 females in the routine group. The two groups had no significant difference in baseline data ($P > .05$). The grade of angina pectoris in both groups was Class II (moderate). Inclusion criteria: (1) meeting the diagnostic criteria for stable angina pectoris[6]; (2)Age 60-80 years old (Set the upper limit at 80 years old mainly takes into account the decline of physical function and drug metabolism ability of elderly patients and the increased risk of other age-related complications. The lower limit of 60 years old is to ensure that the subjects have a relatively stable disease state and sufficient life expectancy to evaluate the impact of treatment on long-term prognosis); (3) be mentally competent and able to communicate effectively; (4) The treatment compliance is strong; (5) Complete data, be informed of the study, and sign the consent form. Exclusion criteria: (1) Those who do not meet the above standards; (2) Patients undergoing percutaneous coronary intervention; (3) New York Heart Association (NYHA) heart function grade IV patients; (4) Patients with non-ischemic chest pain; (5) Patients with severe abnormalities of liver, kidney and hematopoietic system combined with malignant tumors; (6) Unable to fully participate in this study. The research scheme has been strictly examined and approved by the Scientific Review Committee.

Methods

Both groups were given conventional drug intervention, including oral Baiaspirin 100 mg/d (Bayer, Sinomedical approval number H20130339), atorvastatin calcium 20 mg/d, The initial dose is 20mg/ day, which can be adjusted appropriately according to the patient's blood lipid level, and can be increased to 80mg/ day at most (Pfizer, Sinomedical approval number H20051408), isosorbide mononitrate 40 mg/d (LeP, National medicine approval number H20066203).

The nicodil group was given nicodil orally based on conventional treatment, and the drugs were selected by Xi'an Hanfeng Pharmaceutical, National medicine license number H61022860, 5 mg/d, d/3 times. The two groups of subjects continued the intervention for 3 months, and the patients were instructed to pay attention to rest, ensure sleep, and have reasonable exercise and diet.

Observation Indicators

(1) The clinical efficacy of the subjects was observed. Electrocardiogram was marked before medication, 1, 2, 3, 7 days, 1 month, and 3 months after medication, and the baseline changes were observed. Determination criteria: (1) Significant effect: the frequency of angina pectoris was reduced by more than 80%, the duration of heartache was significantly reduced, and the electrocardiogram was normal; (2) Effective: compared with the angina pectoris before the intervention, the number of angina pectoris was reduced by 60%~80%, and the Electrocardiogram (ECG) showed that the ST segment decreased by more than 0.05 mm; (3) Ineffective: the number of angina pectoris attacks was reduced by less than 60% compared with that before the intervention, and there was no significant improvement in ECG detection; Total effective rate = (significant effect + effective)/total number of cases × 100%[7];

(2) The duration and weekly frequency of angina pectoris were analyzed;

(3) The improvement of cardiac function indexes of the subjects was observed, and GE VIVID E9 detected the Left ventricular ejection fraction before and after intervention. LVEF and left ventricular shortening fraction (LVFS);

(4) The improvement of exercise tolerance was analyzed;

(5) The occurrence of adverse reactions such as hypotension, gastrointestinal reactions, and headache were recorded.

(6) Chest pain was evaluated using the Seattle Angina Scale (SAQ).

Table 1. Baseline data analysis of the two groups [$\bar{x} \pm s$ (n, %)]

Project		Nicordil group (n=30)	Regular group (n=30)	t/χ^2	*P* value
Age (years)		71.10±6.01	72.80±6.18	0.843	.417
Gender	Male	17 (56.67)	16 (53.33)	0.754	.546
	Female	13 (43.33)	14 (46.67)		
Systolic blood pressure (mmhg)		134.64±7.89	133.88±9.27	0.344	.732
Diastolic blood pressure (mmhg)		83.78±5.85	86.34±5.30	1.773	.081
Heart rate (beats /min)		68.23±4.60	66.07±3.40	1.943	.057
A family history of		17 (56.67)	15 (45.45)	0.625	.409

Table 2. Comparison of treatment effective rates between the two groups (n, %)

Group	Number of cases	Excellent	Effective	Invalid	Total effective rate
Nicordil group	30	18 (60.00)	10 (33.33)	2 (6.67)	28 (93.33)
Regular group	30	15 (50.00)	7 (23.33)	8 (26.67)	22 (73.33)
χ^2		-	-	-	8.624
P value		-	-	-	<.001

(7) The levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were detected by direct method.

Statistical analysis

Data were processed by Statistic Package for Social Science (SPSS) 26.0 (IBM, Armonk, NY, USA), measurement data were expressed as ($\bar{x} \pm s$), *t* test for data between groups, and *F*-test for data between multiple groups. Count data were expressed as (%), χ^2 test; Repeated measurement ANOVA, analyzed data of each time period between groups and a spherical test was performed. For continuous data, independent sample *t* test was used to compare the differences between the two groups. This method is suitable for two groups of independent data, and it was assumed that the data satisfy normal distribution. Through *t* test, whether the difference between the two groups is statistically significant can be known. $P < .05$ was used to indicate statistical significance.

RESULTS

Baseline Data

By comparison, there were no significant differences in age, gender, blood pressure, heart rate, and other baseline data between the two groups, which were comparable ($P > .05$). Table 1.

Treatment efficiency of the study subjects

The total effective rate of nicorandil group was higher than that of the conventional group ($P < .05$). Table 2.

Duration and number of angina attacks per week

The continuous observation showed that the duration of heart attacks and the frequency of heart attacks per week in nicorandil group were lower than those in the conventional group ($P < .05$). Table 3.

Cardiac function indicators

Regular follow-up showed that there was no significant difference in cardiac function indexes between the two groups before intervention ($P > .05$). The cardiac function indexes of the two groups were significantly improved at 1 month and 3 months after intervention, but the improvement degree of nicorandil group was greater ($P < .05$). Attached Table 4, Figure 1, 2.

Improvement of exercise tolerance

The improvement of exercise tolerance in Nicorandil group was significantly better than that in the conventional group ($P < .05$). Table 5.

Table 3. Comparison of angina pectoris duration and weekly frequency between the two groups ($\bar{x} \pm s$)

Group	Number of cases	Duration of heart attack (min/ time)	Number of episodes per week (times)
Nicordil group	30	3.14±1.10	2.90±1.40
Regular group	30	8.97±1.98	7.20±2.16
t		14.067	9.165
P value		<.001	<.001

Table 4. Comparison of cardiac function indexes between the two groups before, 1 and 3 months after intervention ($\bar{x} \pm s$)

Group	Time	LVEF (%)	LVFS (%)
Nicordil group(n=30)	Before the intervention	47.71±1.43	30.69±1.87
	1 month after intervention	56.69±2.01	34.43±2.78
	3 months after intervention	63.49±2.30	39.97±3.23
Regular group (n=30)	Before the intervention	48.43±1.48	30.14±1.61
	1 month after intervention	50.50±1.86	31.59±2.60
	3 months after intervention	55.44±2.51	35.52±3.05
F_{time}		12.953	5.483
P_{time}		<.001	<.001
$F_{time\ point*group}$		12.367	4.083
$P_{time\ point*group}$		<.001	<.001

Figure 1. Comparison of LVEF between the two groups before and 1 and 3 months after intervention

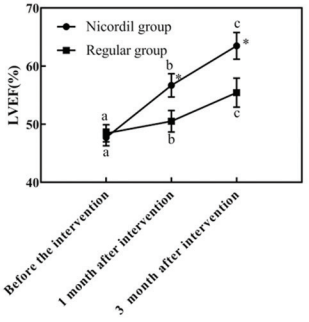

Figure 2. Comparison of LVFS between the two groups before, 1, and 3 months after intervention

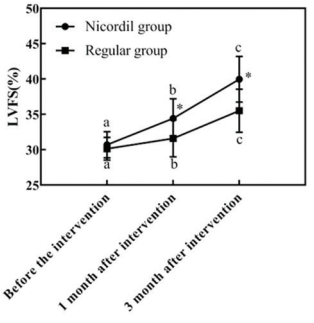

Table 5. Analysis of the improvement of exercise tolerance of the two groups (n, %)

Group	Number of cases	Improve	not improve
Nicordil group	30	26 (86.67)	4 (1.33)
Regular group	30	20 (66.67)	10 (33.33)
χ^2		8.769	7.541
P value		<.001	<.001

Table 6. Comparison of adverse reaction events between the two groups at 3 months follow-up (n, %)

Group	Number of cases	Low blood pressure	Gastrointestinal tract reaction	Have a headache	The total incidence of
Nicordil group	30	1 (3.33)	1 (3.33)	1 (3.33)	3 (10.00)
Regular group	30	2 (6.67)	3 (10.00)	3 (10.00)	8 (26.67)
χ^2		7.541	7.471	6.137	5.431
P value		<.001	<.001	<.001	<.001

Figure 3. Graphs of the incidence of adverse events in the two groups at 3 months of follow-up

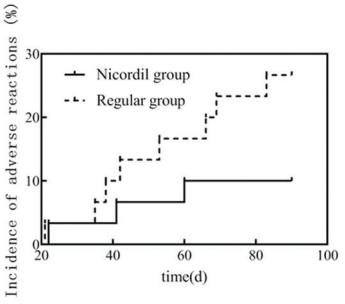

Table 7. Comparison of SAQ scores of subjects ($\bar{x} \pm s$)

Group	Number	SAQ (points)
Nicordil group	30	75.63±5.42
Regular group	30	56.86±3.15
t		9.887
P value		<.001

Table 8. Comparison of HDL-C and LDL-C levels between the two groups ($\bar{x} \pm s$)

Group	Number	HDL-C (mmoL/L)	LDL-C (mmoL/L)
Nicordil group	30	1.87±0.31	2.40±0.25
Regular group	30	1.65±0.30	2.69±0.32
t		8.734	7.355
P value		<.001	<.001

Security

After 43 months of regular follow-up, 3 adverse reactions occurred in the nicorandil group and 8 cases in the conventional group. The safety of nicorandil group was higher than that of the conventional group ($P < .05$). Attached Table 6, Figure 3.

Occurrence of chest pain in subjects

The SAQ score of nicorandil group was significantly better than that of the conventional group ($P < .05$). Table 7.

Serum HDL-C and LDL-C levels

The two groups had statistical differences in blood lipid level and hemorheology ($P < .05$).

DISCUSSION

Coronary atherosclerosis is the main cause of SAP, after which patients will have obvious chest pain and chest discomfort symptoms.[8,9] Moreover, SAP often occurs after physical work, so patients with this disease cannot perform physical work, seriously affecting their daily life and exercise. If not treated in time, they may even suffer from myocardial infarction and death.[10,11]

Conventional treatment can regulate patients' blood lipids, anti-platelet aggregation and improve cardiac function to a certain extent, but the overall effect is not good. Therefore, finding an ideal intervention program is a key problem to be solved at this stage.[12] Nicorandil belongs to nitrate compounds, which have a certain vasodilatation effect, can effectively activate ATP-sensitive potassium channels in vascular smooth muscle cells, and has a certain inhibitory effect on the development of SAP.[13] The results of this study showed that the clinically effective rate of nicorandil group was significantly higher than that of conventional therapy patients. The mechanism was analyzed as follows: Nicorandil, on the one hand, can accelerate the outflow of potassium ions, on the other hand, it can avoid the influx of calcium ions, and release nitric oxide, which can effectively promote the relaxation of vascular smooth muscle, accelerate the dilation of peripheral blood vessels and coronary arteries, lead to the reduction of cardiac load, increase blood flow, and alleviate the clinical effect.[14] Qian G[15] team applied to nicole's intervention in patients with SAP, according to the patient's heart duration and attack number of times a week were lower than conventional intervention patients. As a result, this study suggests that nicole to relief for SAP, angina pectoris, investigate its reason, nicole, can activate the cytoplasm cyclase guanylic acid, promote vascular smooth muscle relaxation, Reduces oxygen consumption in the heart muscle, thereby better protecting the heart and reducing angina pectoris caused by ischemia. Nicorandil can also activate ATP-sensitive potassium channels (KATP) in vascular smooth muscle cells. Potassium channel is the key element to control cell membrane potential, and KATP channel plays an important role in regulating the contraction and contraction of myocardial and vascular smooth muscle cells. Nicorandil can activate KATP channel, trigger depolarization of cell membrane, further inhibit Ca2+ from entering cells, thus relaxing vascular smooth muscle. This mechanism is helpful to reduce the afterload and peripheral vascular resistance of the heart and further improve myocardial perfusion. Nicorandil may be an effective alternative for patients who cannot tolerate nitrate drugs or have drug resistance. In addition, for patients with high risk factors such as hypertension or diabetes, nicorandil may help to reduce the afterload and peripheral vascular resistance of the heart and further improve myocardial perfusion.

LVEF and LVFS can effectively evaluate myocardial contractility, and the higher the value, the stronger the patient's myocardial contractility.[16] This study showed that the improvement of cardiac function indexes and exercise

tolerance of nicorandil group after intervention were significantly better than those of the conventional group, indicating that the application of nicorandil can promote the improvement of cardiac function and exercise tolerance. Based on this analysis, the reasons may be as follows: Nicorandil has a certain inhibitory effect on platelet aggregation, can reduce blood viscosity, improve microcirculation in ischemic area, improve confidence function level, and increase exercise tolerance.[17] In addition, scholars Xu L et al[18] found that the incidence of adverse reactions in the conventional group with conventional treatment was significantly higher than that in the nicorandil group. The data of this study was not significantly different from that of the scholar, which further confirmed the authenticity of the results of this study and also indicated that the application of nicorandil in SAP patients has a certain safety. Nicorandil contains phosphodiesterase 5, which has a certain blocking effect, can produce antihypertensive effect, and will not increase other adverse reactions, and has a certain safety.

Although the results of this study provide valuable insights for the potential application of nicorandil in the treatment of SAP, there are still some limitations. The sample size is relatively small, which may limit the representativeness and statistical validity of the results. In addition, the study time is relatively short, and only the short-term therapeutic effect is observed.

For future research, there are several areas worthy of further discussion. First, larger-scale and longer-term studies are needed to verify the efficacy and safety of nicorandil in the treatment of SAP. Secondly, research on specific patient groups or situations may help to determine the scope of application and potential beneficiaries of nicorandil more accurately. In addition, it is also of great significance to explore the interaction between nicorandil and other drugs and its influence on cardiovascular events.

According to the current research results, nicorandil has certain potential as an adjuvant therapy for SAP. However, due to the limitations of the study and the lack of long-term data, it is impossible to conclude that nicorandil should be regarded as part of the standard treatment of SAP. Therefore, it is suggested that more large-scale and long-term clinical trials should be conducted to further verify the efficacy and safety of nicorandil before it is included in SAP treatment guidelines. Meanwhile, doctors still need to make individual decisions according to the specific situation of patients and existing guidelines when treating SAP.

CONCLUSION

Nicorandil has remarkable clinical efficacy and good safety in the treatment of SAP. Nicorandil may bring multiple benefits to SAP patients by dilating coronary arteries and activating ATP-sensitive potassium channels in vascular smooth muscle cells. This includes improving myocardial perfusion, reducing the frequency of angina pectoris, reducing cardiac afterload and improving the quality of life of patients.

In the real-world clinical environment, the use of nicorandil may provide an effective adjuvant treatment option for SAP patients. It may help patients better control symptoms, reduce the risk of cardiovascular events and improve their quality of life.

In order to further verify the efficacy and safety of nicorandil in the treatment of SAP, it is suggested to conduct a larger and longer-term study. These studies can include in-depth exploration of specific patient groups or situations, as well as research on interactions with other drugs.

For health care professionals, the results of this study provide new treatment strategies and choices. Nicorandil can be considered as an adjuvant therapy in the treatment of SAP patients. However, due to the limitations of the study and the lack of long-term data, it is suggested to use nicorandil cautiously in clinical practice and pay close attention to patients' reaction and safety. According to the current treatment guidelines, doctors still need to make individualized decisions according to the specific conditions of patients when treating SAP. The use of nicorandil should be considered comprehensively with the patient's medical history, complications and other treatment factors. For SAP patients, the use of nicorandil may bring many potential benefits. It can improve myocardial perfusion and reduce the frequency of angina pectoris, thus improving the symptoms and quality of life of patients.

ETHICAL COMPLIANCE

The ethics committee of Nanjing First Hospital approved this study. Signed written informed consent were obtained from the patients and/or guardians.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

XW and HC designed the study and performed the experiments, XW collected the data, HC analyzed the data, XW and HC prepared the manuscript. All authors read and approved the final manuscript.

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