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Original Article

Efficacy and safety of nicorandil monotherapy and nicorandil-clopidogrel combination therapy on cardiac function in patients with coronary heart disease

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Abstract: Objectives: To compare the efficacy and safety of nicorandil monotherapy and nicorandil-clopidogrel combination therapy on cardiac function in patients with coronary heart disease (CHD). Methods: The clinical data of 200 patients with CHD were retrospectively analyzed. The patients were divided into two groups according to different treatment methods. Group A (n = 100) received nicorandil-clopidogrel combination therapy (intravenously injected with 25 mg of nicorandil and orally administered 300 mg of clopidogrel for 3 months), and Group B (n = 100) received nicorandil monotherapy (intravenously injected with 25 mg of nicorandil for 3 months). The primary endpoints included cardiac function indices and ST-segment behavior on electrocardiogram (ECG) before and after treatment. The secondary endpoints included adverse reactions, clinical efficacy, platelet aggregation, activated partial thromboplastin time (APTT), high-sensitivity cardiac troponin T (hs-cTnT), and creatine kinase isoenzyme MB (CK-MB) levels after treatment. Multivariate regression analyses were used to assess the contribution of a single drug to the ultimate outcome. Results: After treatment, both groups exhibited significant decreases in brain natriuretic peptide (BNP) and N-terminal pro-hormone BNP levels compared with before treatment, with the levels significantly lower in Group A than in Group B ($P < 0.05$). After treatment, left ventricular ejection fraction was significantly increased in both groups compared with before treatment, and that was much higher in Group A than in Group B ($P < 0.05$). After treatment, the frequency and duration of ST-segment depression were decreased in both groups compared with before treatment, and they were much lower in Group A than in Group B (all $P < 0.05$). The total incidence of adverse reactions in Group A (4.00%) was slightly lower than that in Group B (7.00%), with no significant difference ($P > 0.05$). Group A (92.00%) had a higher overall response rate than Group B (81.00%) ($P < 0.05$). Conclusion: Nicorandil-clopidogrel combination therapy exhibited enhanced clinical efficacy in patients with CHD. In addition, the combination therapy regulated hs-cTnT and CK-MB levels, which may suggest a better patient prognosis.

Keywords: Coronary heart disease, nicorandil, clopidogrel, combination therapy, cardiac function

Introduction

When atherosclerotic process begin to affect arteries supplying blood to the heart, the condition is called coronary artery disease, which is one of a variety of cardiovascular diseases characterized by cardiac dysfunction and is more common in middle-aged and elderly people [1]. Coronary heart disease (CHD) is a condition primarily induced by atherosclerosis. It is a process in which the plaque builds up in the walls of arteries that supply blood to the coronary arteries, leading to the narrowing inside of the arteries over time, which can partially or totally block the blood flow, subsequently resulting in reduced oxygen.

Due to continuous changes in living standards and habits, the total incidence of cardiovascular diseases is soaring, with an increased incidence among young individuals [2]. CHD has a high morbidity and mortality rate and must be diagnosed and treated promptly, otherwise it may lead to serious consequences such as sudden death and heart failure [3, 4]. For CHD patients complicated with hyperlipidemia,

hypertension, and other risk factors, surgical treatment is the main option of clinical treatment, among which minimally invasive surgery is the first choice; for patients whose prognosis and conditions do not meet surgical standards, drug therapy can effectively control the disease progression [5, 6].

Nicorandil is a nicotinamide derivative that dilates arteries and veins and reduces the cardiac load by activating adenosine triphosphate-sensitive potassium channels. In this way, it can reduce the risk of cardiovascular diseases, help heart failure patients control their disease progression, and relieve pain. Nicorandil improves the arterial blood flow rate by controlling the flow of K^+ and Ca^{2+} inside and outside cells, increasing vascular smooth muscle relaxation and reducing the occurrence of coronary artery spasms and expansion [7, 8]. However, nicorandil monotherapy has been reported to be less effective in areas other than symptom relief in patients with CHD [9, 10]. The other drug in the study, clopidogrel, is an antiplatelet drug widely used in the treatment of myocardial infarction, stroke, and peripheral arterial disease. It is incorporated into the conservative therapeutic regimen of patients with CHD to strengthen their immune system, restore vascular elasticity, and protect renal function [11, 12].

The purpose of this study was to compare the clinical efficacy and safety of nicorandil monotherapy and nicorandil-clopidogrel combination therapy on cardiac function in patients with CHD, so as to provide more scientific ideas and methods for clinical treatment.

Materials and methods

Study design and patient selection

The clinical data of patients with CHD admitted to Ganzhou People's Hospital from January 2020 to October 2022 were retrospectively analyzed. Finally, the medical history and treatment history of a total of 200 patients with CHD who met the inclusion criteria were included. Among them, 100 patients were treated with nicorandil combined with clopidogrel, who were set as Group A; and there were 100 patients treated with nicorandil alone, set as Group B.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients with coronary atherosclerotic heart disease who were diagnosed with stable angina or unstable angina; (2) those whose cardiac function NYHA was classified as I-III, and with a course of disease of more than 5 years; (3) patients who were aged 18 to 89 years; (4) patients who were treated with nicorandil or clopidogrel in combination with nicorandil; (5) those with good verbal and written communication skills and normal intelligence.

Exclusion criteria: (1) patients who had suffered from acute ST-segment elevation myocardial infarction in the past; (2) those with poor hypertension control (systolic blood pressure ≥ 160 mmHg, or diastolic blood pressure ≥ 100 mmHg); (3) those who suffered from serious diseases of other systems; (4) those who had a history of mental illness or cognitive impairment; (5) those with incomplete medical records.

Ethics approval was obtained from the Medical Ethics Committee of Ganzhou People's Hospital.

Data extraction and validation

The medical records of each patient were reviewed in the medical record system, and the present medical history, past history, personal history, admission and discharge diagnosis, as well as the results of various laboratory and auxiliary examinations were reviewed and recorded in detail, including: admission age (defined as old age according to whether ≥ 65 years old), gender, height and body mass (calculated body mass index, BMI), admission blood pressure and heart rate and related symptoms, history of smoking and drinking, history of hypertension, diabetes, cerebrovascular disease, history of dyslipidemia, history of renal dysfunction, family history; routine blood work, blood biochemistry, liver and kidney function, myocardial enzyme profile, cardiac ultrasound and other relevant tests and examination results after admission.

According to the medical records, any patient records that did not match the inclusion criteria of this study were excluded.

Outcome measures

The primary outcome measures were the change in cardiac function indices and ECG findings before and after treatment. Secondary outcome measures included treatment efficacy (high efficacy, good efficacy, or no efficacy), incidence of adverse reactions, platelet aggregation time, activated partial thromboplastin time (APTT), and levels of hs-cTnT and CK-MB.

Reagents and materials

Nicorandil was purchased from Beijing Sihuan Kebao Pharmaceutical Co., Ltd. with SFDA approval No. H20120069; clopidogrel was purchased from Sanofi Winthrop Industrie with SFDA approval No. J20130083; angiographic catheters were purchased from Qisheng Medical Devices Co., Ltd.; plasma separators were purchased from Shanghai Runhe Environment Protection Technology Co., Ltd.; Developer was purchased from Shanghai Regal Biotechnology Development Co., Ltd.; and a microplate reader was purchased from HT Instruments.

Cardiac function index, ECG and ELISA findings

Cardiac function was detected with left ventricular angiography in all patients before and after treatment. A catheter was inserted into the 30° projection of the right anterior oblique of the left ventricle, and 30 mL of contrast medium was injected at a rate of 12-15 mL/s to determine the left ventricular ejection fraction (LVEF). The duration and frequency of ST-segment depression were assessed using continuous 12-lead dynamic ECG monitoring for 24 hours at baseline and after 3 months of treatment. During the 24-hour monitoring period, the ECG data were recorded and analyzed to determine the total duration and incidence of ST-segment depression events. New York Heart Association (NYHA) functional classification was used to grade the cardiac function.

The expression levels of brain natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and creatine kinase MB (CK-MB) were detected using ELISA. Fasting venous blood (5 mL) was drawn from each patient and centrifuged at 3,000 rpm for 8 min at room temperature. The serum was then stored in a freezer at -80°C for further evaluation. Next, 100 μL of serum samples from the two groups were added to a well plate coated with anti-BNP antibodies at 37°C for 90 min. After reaction, the liquid was discarded, and the plate was dried and washed three times. Subsequently, the color reaction was allowed to proceed with 150 μL of developer at 37°C for 30 min. The average optical density of a 50-μL sample from each well was measured and recorded at 500 nm using a microplate reader. The detection of NT-proBNP, hs-cTnT, and CK-MB was performed using the same procedure, in strict accordance with the instructions of the ELISA kits.

Statistical analysis

Statistical data analyses were performed using Statistical Package for Social Sciences (SPSS) statistics version 19.0 (IBM Corp., Armonk, NY, USA). A chi-square test was used for the comparison of counting data (n, %), a t-test was conducted for comparison of measurement data (mean ± SD) between the groups, and a paired t-test was used for the same index before and after treatment in the same group. The data obtained were visualized using Graphpad Prism 8 (GraphPad Software, San Diego, CA, USA). Multivariate regression analyses were used to assess the contribution of a single drug to the ultimate outcome. A statistically significant difference was considered at $P < 0.05$.

Results

General characteristics

Eligible patients included 146 males and 54 females, with a mean age of (62.43 ± 14.73) years old and a mean body mass index (BMI) of (23.73 ± 3.64) kg/m^2. Among these patients, there were 86 cases with acute myocardial infarction, 34 cases with previous myocardial infarction, 15 cases with valve history, and 65 cases with angina pectoris. There was no significant difference in sex, age, BMI, chest pain, heart failure, or left ventricular angiography between the two groups (all $P > 0.05$), as shown in **Table 1**.

Comparison of cardiac function indices

There were no significant differences in BNP levels, NT-proBNP levels, or LVEF between the

Table 1. Comparison of general characteristics

General data	Group A (n = 100)	Group B (n = 100)	χ^2/t	*P*
Sex (cases)			0.102	0.750
Male	72 (72.00)	74 (74.00)		
Female	28 (28.00)	26 (26.00)		
Age (years)	62.63 ± 14.99	61.82 ± 14.63	0.387	0.699
BMI (kg/m^2)	24.03 ± 3.75	23.66 ± 3.69	0.703	0.483
Chest pain (cases)			0.117	0.733
Yes	77 (77.00)	79 (79.00)		
No	23 (23.00)	21 (21.00)		
Heart failure (cases)			0.237	0.627
Yes	24 (24.00)	27 (27.00)		
No	76 (76.00)	73 (73.00)		
Left ventricular angiography (cases)			0.189	0.663
Abnormal	87 (87.00)	89 (89.00)		
Normal	13 (13.00)	11 (11.00)		
Pathological Typing (cases)			0.246	0.970
Acute myocardial infarction	44 (44.00)	42 (42.00)		
Old myocardial infarction	16 (16.00)	18 (18.00)		
Valve history	8 (8.00)	7 (7.00)		
Angina pectoris	32 (32.00)	33 (33.00)		

BMI: body mass index.

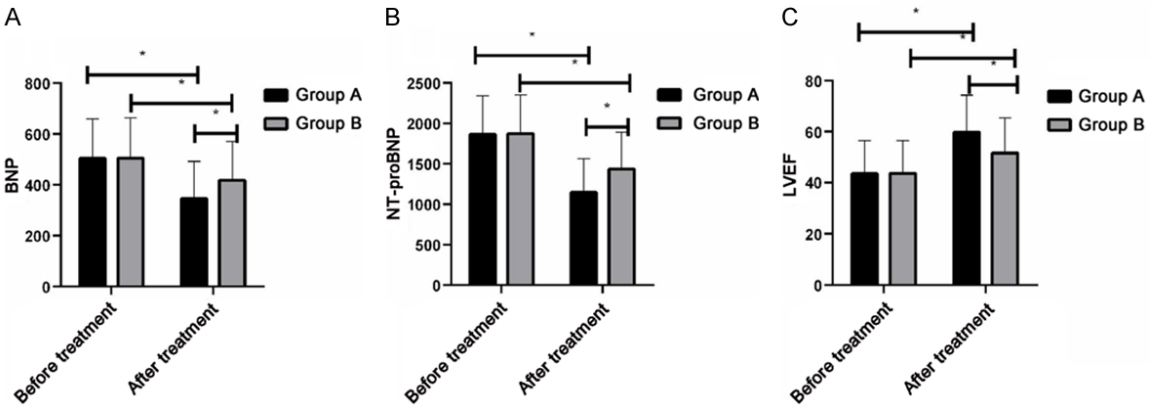

Figure 1. Comparison of the cardiac function indices between the two groups. A: BNP level was decreased in both groups after treatment and was much lower in Group A than in Group B. B: NT-proBNP level was decreased in both groups after treatment and was much lower in Group A than in Group B. C: LVEF was increased after treatment in both groups and was much higher Group A than in Group B. Note: BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; LVEF: left ventricular ejection fraction. *, $P < 0.05$.

two groups before treatment (all $P > 0.05$). After treatment, both groups showed a significant decrease in BNP and NT-proBNP levels and a significant increase in LVEF, and Group A showed lower BNP and NT-proBNP levels and higher LVEF than Group B, exhibiting significant difference (all $P < 0.05$) (**Figure 1**).

Comparison of ECGs

There were no significant differences in frequency and duration of ST-segment depression between the two groups before treatment (all $P > 0.05$). After treatment, frequency and duration of ST-segment depression decreased in

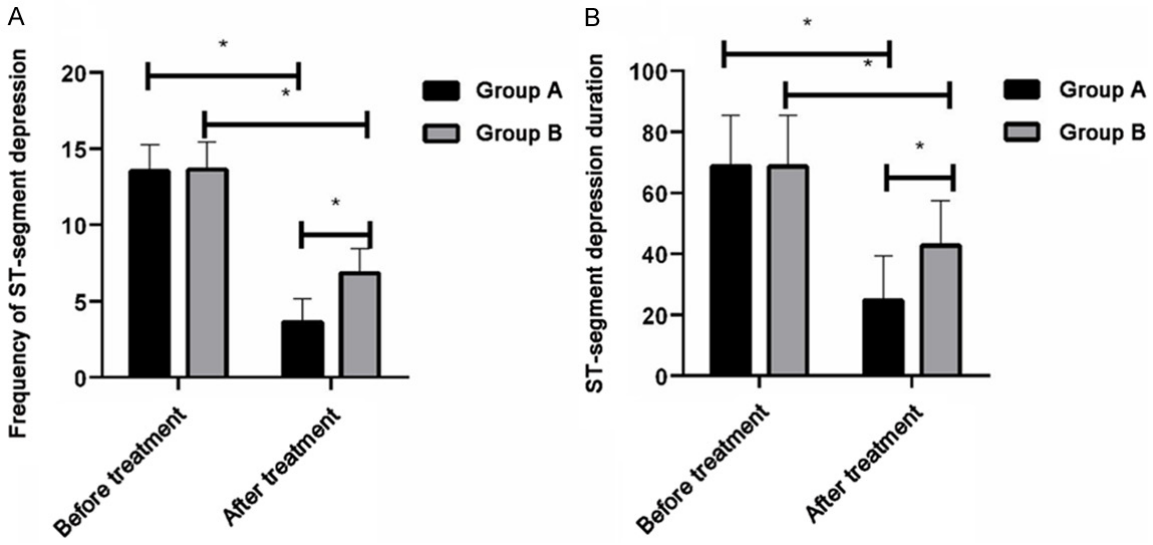

Figure 2. Comparison of ECG between two groups. A: The frequency of ST-segment depression was reduced in both groups after treatment and was much lower in Group A than in Group B. B: ST-segment depression duration was reduced in both groups after treatment and was much lower in Group A than in Group B. Note: ECG: electrocardiogram. *, $P < 0.05$.

Table 2. Comparison of the incidence of adverse reactions [n (%)]

Adverse reactions	Group A (n = 100)	Group B (n = 100)	χ^2	*P*
Nausea and vomiting	1 (1.00)	2 (2.00)	-	0.916
Dizziness	0	1 (1.00)	-	0.876
Gastrointestinal reaction	1 (1.00)	1 (1.00)	-	0.999
Liver and kidney abnormalities	2 (2.00)	3 (3.00)	-	0.743
Total incidence of adverse reactions	4 (4.00)	7 (7.00)	0.866	0.352

Table 3. Comparison of clinical efficacy [n (%)]

	Group A (n = 100)	Group B (n = 100)	χ^2	*P*
High efficacy	62 (62.00)	42 (42.00)	-	-
Good efficacy	30 (30.00)	39 (39.00)	-	-
No efficacy	8 (8.00)	19 (19.00)	-14.23	-0.011
Overall response rate	92 (92.00)	81 (81.00)	5.181	0.023

both groups, with Group A being significantly lower than Group B (all $P < 0.05$) (**Figure 2**).

Comparison of adverse reactions

The total incidence of adverse reactions in Group A was slightly lower than that in Group B, but the difference was not statistically significant ($P > 0.05$) (**Table 2**).

Comparison of clinical efficacy

The overall response rate in Group A (92%) was statistically higher than that in Group B (81%) ($P < 0.05$) (**Table 3**).

Comparison of coagulation function after treatment

After treatment, the duration of platelet aggregation in Group A was lower than that in Group B, but the APTT was higher than that in Group B, and the difference was statistically significant (all $P < 0.05$) (**Table 4**).

Comparison of hs-cTnT and CK-MB levels after treatment

After treatment, the levels of hs-cTnT and CK-MB in Group A were lower than those in

Table 4. Comparison of the coagulation function after treatment

Coagulation function	Group A (n = 100)	Group B (n = 100)	*t*	*P*
Platelet aggregation duration (min)	0.29 ± 0.05	0.47 ± 0.07	20.920	< 0.001
APTT (min)	47.83 ± 7.62	39.54 ± 7.52	7.743	< 0.001

APTT: activated partial thromboplastin time.

Table 5. Comparison of hs-cTnT and CK-MB levels after treatment

Parameters	Group A (n = 100)	Group B (n = 100)	*t*	*P*
hs-cTnT (pg/mL)	13.45 ± 0.83	19.35 ± 0.91	47.900	< 0.001
CK-MB (U/L)	23.95 ± 0.92	33.25 ± 1.15	63.150	< 0.001

hs-cTnT: high-sensitivity cardiac troponin T; CK-MB: creatine kinase isoenzyme MB.

Group B, and the difference was statistically significant (all $P < 0.05$) (**Table 5**).

Multivariate regression analysis

To assess the impact of individual drugs on efficacy, multivariate regression analysis was used. First of all, the result calculated by Durbin Watson test was 1.922, which was between 1 and 4. Therefore, it could be considered that the data conformed to independence and the regression fit was good. The results of regression analysis of the efficacy of nicorandil were b = 0.36, β = 0.256, $P < 0.001$, the results of regression analysis for the efficacy of clopidogrel were b = 0.73, β = 0.318, $P < 0.001$. The results suggested that clopidogrel was more effective in patients and promoted a better prognosis for patients.

Discussion

Coronary heart disease (CHD) can induce a range of myocardial and histological complications [13-15]. The clinical symptoms include anterior cardiac pain, chest tightness, and dyspnea [16, 17]. Beta-receptor agonists and nitrates are often used clinically to improve coronary oxygen supply and reduce oxygen consumption [18, 19]. Nicorandil is a nitrate compound which can effectively solve the cardiac functional decline caused by myocardial ischemia. Clopidogrel affects liver metabolism. Metabolic active substances bind to corresponding receptors on the surface of platelets to block adenosine diphosphate, thus reducing adverse pathological manifestations, such as platelet aggregation and thrombosis [20, 21]. Since both nicorandil and clopidogrel ensure blood flow supply, the effects of their combination on the cardiac function of patients were explored to determine effective preventive measures to reduce adverse cardiovascular events.

The results in this study found that the levels of BNP and NT-proBNP were reduced in both groups after treatment and were much lower in the combined treatment group. The underlying mechanism may be as follows. Similar studies have found that in patients with heart failure, ventricular pressure and volume markedly increased, and BNP and NT-proBNP were synthesized and secreted in large quantities from the ventricles due to excessive pressure, which is related to antihypertensive and diuretic therapies [22, 23].

It was also found that LVEF increased in both groups, and was much higher in Group A than in Group B; after treatment, the duration and frequency of ST-segment depression decreased in both groups, and were much lower in Group A than in Group B. These findings suggested that the combination therapy could more effectively improve LVEF. The underlying mechanism may be that LVEF is the measurement of blood pumped from the left ventricle of the heart with each contraction to further reflect the myocardial functional cell count. The lower the LVEF, the greater the percentage of fibrosis and myocardial necrosis, and the worse the cardiac muscle contractility [24]. When cardiac contraction is decreased, myocardial metabolism is weakened, with more lactic acid and less oxygen consumption achieved, while the duration and frequency of ST-segment depression are increased in ECG [25].

Group A had lower levels of hs-cTnT and CK-MB than Group B. Studies found that myocardial cell injury caused by metabolic disorders, inflammation, and immune responses may lead to elevated levels of hs-cTnT and CK-MB [26, 27].

Meanwhile, this study found that the combination therapy could reduce the incidence of myocardial ischemia in patients with CHD. Previous studies have shown that [28, 29] cardiac function is significantly reduced in patients with myocardial ischemia-induced CHD. When the body responds to chronically inadequate peripheral tissue perfusion by activating the renin-angiotensin-aldosterone system (RAAS), imaging test shows ventricular dilatation and even remodeling, and focal contractions. Consistent with the results of previous studies, this study demonstrated that the combination therapy could restore and protect cardiac function and reduce factors that cause myocardial cell injury. Group A showed a significantly higher overall response rate and a slightly lower total incidence of adverse reactions than Group B. The results indicated that combined therapy had a higher efficacy, better efficacy, and higher safety than the nicorandil monotherapy, and the total incidence of adverse reactions did not increase significantly. Besides, the coagulation function of Group A was better than that of Group B after treatment. According to a previous study [30], patients with cardiovascular diseases usually have some changes in coagulation and fibrinolysis systems, resulting in an unstable dynamic environment, increased levels of coagulation factors, and decreased anticoagulant and fibrinolytic activities. Restoring the coagulation function contributes to better recovery. The combination therapy was safer and more efficient, and had a stronger anticoagulation effect, which helped inhibit platelet activation and aggregation and prevent the spread of thrombosis and thrombosis itself.

In addition to the benefits provided by nicorandil, the combination therapy with clopidogrel may offer further advantages due to clopidogrel's antiplatelet properties. Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist that inhibits platelet aggregation by irreversibly binding to the P2Y12 receptor on platelets [31]. By blocking the activation of the glycoprotein IIb/IIIa receptor, clopidogrel prevents fibrinogen binding and platelet cross-linking, ultimately reducing the risk of thrombus formation and ischemic events in patients with CHD [32].

Moreover, studies have suggested that clopidogrel may exert additional cardioprotective effects beyond its antiplatelet activity. These effects include improvement of endothelial function, reduction of inflammation, and mitigation of oxidative stress [33, 34]. In the context of our study, these pleiotropic effects of clopidogrel may have contributed to the observed improvements in cardiac function, decreased duration and frequency of ST-segment depression, and lower levels of hs-cTnT and CK-MB in Group A compared to Group B. We acknowledge that further investigation is required to elucidate the specific mechanisms underlying the observed benefits of clopidogrel in combination with nicorandil for CHD patients. Future studies can explore the roles of endothelial function, inflammatory markers, and oxidative stress in the context of this combination therapy.

In summary, for patients with CHD, nicorandil-clopidogrel combined therapy can significantly improve cardiac function, with high safety, high efficacy, and high anticoagulation, and may be widely used in clinical application. However, this study still has some limitations, such as the failure to detect inflammatory factors. Since inflammatory responses considerably affect the onset of coronary atherosclerosis, it is necessary to detect inflammatory factors in patients after administration to resolve the efficacy errors caused by inflammatory responses and determine a better therapeutic scheme during efficacy exploration.

Disclosure of conflict of interest

None.

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