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*Original Article*

# Clinical efficacy of high-dose Metoprolol combined with Nicorandil in patients with unstable angina pectoris

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**Abstract:** Objective: To explore the effect of high-dose Metoprolol combined with Nicorandil on unstable angina pectoris. Methods: 84 patients with unstable angina pectoris admitted to our hospital (February 2018 to February 2020) were selected and randomly set as control group (n=92, treated with Nicorandil) and observation group (n=92, treated with high-dose Metoprolol combined with Nicorandil). The efficacy, angina score, angina attack, adverse reactions and Left Ventricular Ejection Fraction (LVFE) of two groups were recorded and compared. Results: (1) The observation group saw dramatically higher total effective rate than the control group (P<0.05). (2) The total SAQ score, DP, TS, AF, AS and PL score were not obviously different in the two groups before treatment (P>0.05). After treatment, the total score, DP, TS, AF, AS and PL score increased, and the increase in observation group was more evident (P<0.05). (3) The frequency and duration of angina attacks were basically the same in the two groups before treatment (P>0.05). After treatment, the frequency and duration of angina pectoris decreased remarkabley in the observation group (P<0.05). (4) The total incidence of adverse reactions in the observation group was higher in comparison with the control group, but no statistical difference was noted (P>0.05). (5) The LVEF of the observation group was higher than that of the control group (inter-group effect: F=421.100, P<0.001), and the LVEF of both groups increased with time (time effect: F=521.700, P<0.001), there was an interaction effect between grouping and time (interaction effect: F=72.650, P<0.001). Conclusion: High-dose Metoprolol combined with Nicorandil is effective in treating unstable angina pectoris, which can effectively reduce the frequency and duration of angina pectoris attacks, and improve patients' heart function, quality of life and body function, with few adverse reactions and thus, with high clinical application value.

**Keywords:** Metoprolol, nicorandil, unstable angina pectoris, clinical efficacy

## Introduction

Angina pectoris, a kind of coronary syndrome, is caused by insufficient coronary blood supply, severe temporary ischemia and hypoxia of the myocardium. It mainly manifests as chest discomfort or chest pain, which usually attacks unexpectedly and generally lasts 3-5 min/time [1, 2]. Angina pectoris can be induced by acute circulatory failure, overstrain, emotional agitation, changeable weather, and satiety [3]. Unstable angina pectoris is an acute manifestation, and its typical pathological cause is unstable coronary plaque (can rupture at any time). Unlike stable angina pectoris, the unstable one is characterized by acute onset, fast progression, and high risk of developing into acute myocardial infarction [4]. Therefore, the primary purpose of clinical treatment of unstable angina is to assist patients to improve the stability of coronary plaques at present. Due to the fact that the stability of coronary plaques is affected by local platelet activity and its aggregation and inflammatory factors, stabled plaque, anti-platelet aggregation and anti-inflammatory are required in unstable angina treatment. Currently, Nicorandil is often applied as an adjuvant drug for unstable angina, which, as a nitrate drug with an effect of opening potassium ion channel. It can reduce the level of calcium ion through activating guanylate-activating enzymein cells, thereby relaxing the vascular

**Table 1.** Comparison of basic data

| Groups | Sex [n (%)] | | Age | Course of disease | BMI |
|---|---|---|---|---|---|
| | Male | Female | ($\bar{x}$±s, years) | ($\bar{x}$±s, years) | ($\bar{x}$±s, kg/m$^2$) |
| Control group (n=92) | 52 (56.52) | 40 (43.48) | 58.32±5.14 | 8.57±4.33 | 23.07±3.05 |
| Observation group (n=92) | 55 (59.78) | 37 (40.22) | 56.47±5.39 | 7.48±4.16 | 22.58±3.14 |
| $\chi^2$/t | 0.201 | | 0.313 | 1.741 | 1.074 |
| *P* | 0.654 | | 0.755 | 0.083 | 0.284 |

smooth muscle and dilating the coronary artery. In addition, Nicorandil also possesses anti-inflammatory, anti-oxidation and endothelium protective functions. However, Nicorandil has adverse reactions such as inducing mucosal ulcer, and it easily leads to hemorrhage and infection in patients [5-7], so there is still risk in the clinical application of Nicorandil in the treatment of unstable angina, and further in-depth research is needed. Therefore, the clinical efficacy of high-dose Metoprolol combined with Nicorandil for unstable angina pectoris was investigated in this study.

## Materials and methods

### *General materials*

The patients with unstable angina pectoris in our hospital (February 2018 to February 2020) were selected. Inclusion criteria: ① patients who met the criteria in *Guidelines for the Diagnosis and Treatment of Unstable Angina Pectoris and non-ST-segment Elevation Myocardial Infarction* [8]; ② patients without enzymatic changes in myocardial infarction; ③ patients with an allergic reaction related to the drugs in this study; ④ patients who have not been used the relevant drugs of this study in the past month or the same period; ⑤ patients who signed an informed consent. Exclusion criteria: ① patients with severe hypertension, systolic blood pressure >200 mmHg (26.6 kpa); ② patients with autoimmune diseases and malignant tumors; ③ patients with severe insufficiency of important organs such as lung, heart, kidney and liver; ④ patients with cerebral hemorrhage or cerebral infarction; ⑤ patients who presented a tendency of blood disease and bleeding; ⑥ patients with angina pectoris of non-coronary heart disease. This study was approved by our hospital ethic committee. A total of 184 cases were included and divided into a control group (n=92) and an observation group (n=92) using a random number table method. There were 57 males and 27 females; the average age was 57.64±5.24 years; the average course of disease was 8.04±5.21 years; the average BMI was 22.87±3.10 kg/m$^2$. The basic data were basically the same such as gender, age, course of disease, body mass index, etc. (P>0.05). See **Table 1**.

### *Treatment schemes*

*Basic treatment:* Both groups received the same routine treatment, using the same diuretic, ACEI, nitrate, digitalis and other drugs.

*Control group:* Patients were given Nicorandil Tablets (SIGMA) under the premise of receiving basic treatment (producer: Nipro Pharma Corporation Kagamiishi Plant; approval number: H20160540; specifications: 5 mg/tablet), oral administration, 1 piece/time, 3 times/d.

*Observation group:* Patients received high-dose Metoprolol Tartrate Sustained-release Tablets based on the procedures in the control group (producer: AstraZeneca Pharmaceutical Co., Ltd.; approval number: Sinopharm J20150044; specifications: 47.5 mg/tablet), oral administration, 2 tablets/d. Both groups were treated continuously for 2 months.

### *Outcome measures*

(1) Clinical efficacy was evaluated and classified. Ineffective: the number of angina attacks reduced by >50%, and the electrocardiogram changes were not obvious. Improved: the number of angina attacks dropped by 50%-80%, and the ECG showed ST segment elevation >1.0 mm but not normal, body posture T wave inversion restored or shallowness >50%. Markedly effective: the patient's angina pectoris basically or completely disappeared, electrocardiogram showed ST segment reached normal, body posture T wave inversion restored. Total effective rate = (improved + markedly

**Table 2.** Comparison of clinical efficacy [n (%)]

| Groups | Ineffective | Improved | Markedly effective | Total effective rate |
|---|---|---|---|---|
| Control group (n=92) | 31 (33.70) | 33 (35.87) | 28 (30.43) | 61 (66.30) |
| Observation group (n=92) | 15 (16.30) | 45 (48.92) | 32 (34.78) | 77 (83.70) |
| $\chi^2$ | | | | 7.42 |
| *P* | | | | 0.006 |

effective) number of cases/total cases × 100% [9]. (2) Angina was scored using Seattle Angina Questionnaire (SAQ). It was measured from five specific aspects: disease perception (DP), treatment satisfaction (TS), angina frequency (AF), and angina stability (AS) and physical limitation (PL), totaling 19 items, with a full score of 100 points. The score was directly proportional to the patient's quality of life and body function [10]. (3) Angina attacks was counted per week before and after treatment (unit: times) and the duration of each angina attack (unit: min) was recorded. (4) Drug-related adverse reactions was recorded that occurred during the treatment, including gastrointestinal reactions, hypotension, tinnitus, headache, dizziness, reflex tachycardia, facial flushing, etc. (5) Left Ventricular Ejection Fraction (LVFE) was detected before and after 2 months, 3 months, 4 months of treatment. LVFE refers to the percentage of the output of the heart per beat in the volume of the left ventricular end-diastolic volume. The normal range of LVFE is 50%-70%, less than 50% indicates that the patient has left ventricular systolic dysfunction, and the higher the LVFE, the better the heart function [11].

*Statistical methods*

SPSS 20.0 software was employed in present study. Qualitative data was represented by n (%), and conducted by $\chi^2$ test, and when 1≤ theoretical frequency <5, chi-square value was the correction value. Quantitative data was represented by x±s, and conducted by t test between the two groups, and repeated measurement analysis of variance was used for data comparison at different time points between the groups. P<0.05 represented a significant difference.

## Results

*Comparison of the efficacy*

The total effective rate in the observation group was dramatically higher than it was in the control group (P<0.05, **Table 2**).

*Comparison of SAQ score before and after treatment between the two groups*

The total SAQ score, DP, TS, AF, AS and PL score were not obviously different in the two groups before treatment (P>0.05). After treatment, the total score, DP, TS, AF, AS and PL score increased, and the increase in observation group was more evident (P<0.05). See **Table 3**.

*Comparison of angina attacks before and after treatment between the two groups*

The frequency and duration of angina attacks was basically the same in the two groups before treatment (P>0.05). After treatment, the frequency and duration of angina pectoris decreased, and the observation group was more remarkable (P<0.05). See **Table 4**.

*Comparison of the occurrence of adverse reactions between the two groups*

Higher total incidence of adverse reactions was seen in the observation group in comparison with the control group, and no statistical difference was marked (P>0.05). See **Table 5**.

*Comparison of LVEF*

Higher LVEF was observed in the observation group compared with the control group (intergroup effect: F=421.100, P<0.001), and the LVEF of both groups increased with time (time effect: F=521.700, P<0.001), there was an interaction effect between grouping and time (interaction effect: F=72.650, P<0.001). See **Table 6** and **Figure 1**.

## Discussion

If unstable angina patients not being treated timely, the disease will aggravate rapidly, and eventually lead to acute myocardial infarction or even sudden death and other critical events, which poses a great threat to the patient's life [12]. Statistics showed that up to 30% of unstable angina patients always affected by myocar-

**Table 3.** Comparison of SAQ score before and after treatment (point, $\bar{x}\pm s$)

| Groups | Control group (n=92) | | Observation group (n=92) | |
|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment |
| Total score | 46.78±8.79 | 58.71±7.55[a] | 47.61±8.67[b] | 66.82±8.34[c] |
| DS | 6.94±2.57 | 8.75±1.28[a] | 7.02±2.23[b] | 9.53±1.32[c] |
| TF | 8.76±2.23 | 11.78±1.95[a] | 9.45±2.16[b] | 14.27±2.04[c] |
| AF | 5.57±1.39 | 6.73±1.31[a] | 5.84±1.64[b] | 7.53±1.34[c] |
| AS | 1.85±0.26 | 2.76±0.27[a] | 1.88±0.31[b] | 3.38±0.32[c] |
| PL | 23.66±3.17 | 28.69±2.48[a] | 23.42±4.06[b] | 32.11±2.57[c] |

Note: [b]represents comparison with that before treatment in control group, $P>0.05$; [a]represents comparison with that before treatment in intragroup, $P<0.05$; [c]represents comparison with that before treatment in intragroup, $P<0.05$; [c]represents comparison with that after treatment in control group, $P<0.05$.

**Table 4.** Comparison of attacks before and after treatment ($\bar{x}\pm s$)

| Groups | Frequency of attacks (times/week) | | Duration of attacks (min/time) | |
|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment |
| Control group (n=92) | 10.45±3.01 | 6.14±1.26* | 6.84±1.37 | 4.82±1.17* |
| Observation group (n=92) | 10.33±3.04 | 3.02±0.27* | 7.13±0.97 | 2.46±0.48* |
| t | 0.269 | 23.224 | 1.657 | 17.900 |
| *P* | 0.788 | <0.001 | 0.099 | <0.001 |

Note: *indicates that compared with that before treatment, $P<0.05$.

**Table 5.** Comparison of adverse reactions [n (%)]

| Groups | gastrointestinal reactions | hypotension | tinnitus | headache | dizziness | reflex tachycardia | facial flushing | Total adverse reaction rate |
|---|---|---|---|---|---|---|---|---|
| Control group (n=92) | 1 (2.38) | 1 (2.38) | 2 (4.76) | 2 (4.76) | 2 (4.76) | 0 (0) | 0 (0) | 8 (19.05) |
| Observation group (n=92) | 1 (2.38) | 1 (2.38) | 2 (4.76) | 1 (2.38) | 2 (4.76) | 2 (4.76) | 3 (7.14) | 12 (28.57) |
| $\chi^2$ | | | | | | | | 0.898 |
| *P* | | | | | | | | 0.343 |

**Table 6.** Comparison of LVEF ($\bar{x}\pm s$)

| Groups | before treatment | 2 months after treatment | 3 months after treatment | 4 months after treatment | F | P |
|---|---|---|---|---|---|---|
| Control group (n=92) | 42.84±3.20 | 50.22±2.20 | 54.71±3.42 | 60.55±3.52 | 524.578 | <0.001 |
| Observation group (n=92) | 42.79±3.24 | 53.88±2.72 | 57.84±3.20 | 65.37±3.50 | 807.747 | <0.001 |
| τ | 0.105 | 10.035 | 6.41 | 9.314 | | |
| *P* | *0.916* | *<0.001* | *<0.001* | *<0.001* | | |

dial infarction within 3 months following the attack, and it is manifested as severe symptoms including significant decrease in cardiac pumping function, abnormally enlarged ventricular volume, and a spherical change in the heart [13, 14].

Metoprolol is a β1 receptor blocker that selectively inhibits the β1 receptor on the heart, reduces the release of renin and slows the heart rhythm, and regulates blood pressure by blocking the renin-angiotensin system, which in turn decreases blood pressure, slows down heart rate, reduces myocardial oxygen consumption, relieves myocardial ischemia symptoms, improves the stability of coronary plaques, and ultimately stabilizes the condition of patients with unstable angina [15-17]. The current study demonstrated that the total effective rate was higher in the observation group than that in the control group, indicating that, high-dose Metoprolol combined with Nicoran-

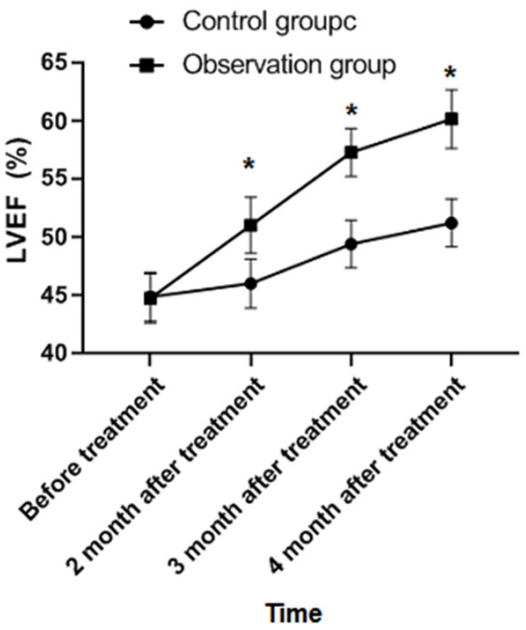


**Figure 1.** Comparison of LVEF between the two groups, *$P$<0.05.

dil can impressively improve the therapeutic effect of unstable angina compared with Nicorandil alone. After treatment, the observation group's total score, DP, TS, AF, AS and PL score were significantly higher than the control group, indicating that high-dose Metoprolol combined with Nicorandil can improve the patient's angina score to optimize the patient's quality of life and body function. After treatment, the frequency and duration of angina pectoris in the observation group were lower than they were in the control group, suggesting that after receiving high-dose Metoprolol combined with Nicorandil, the number of angina pectoris attacks per week decreased significantly, and the duration of each attack was significantly shortened. The incidence of total adverse reactions was not significantly different in two groups, which indicates that the supplement of high-dose Metoprolol on the basis of Nicorandil to treat unstable angina pectoris slightly affects the adverse reactions and the treatment is safe. Compared with the control group, the LVEF at each time point in the observation group after treatment was remarkably higher, which suggests that high-dose Metoprolol combined with Nicorandil can significantly improve the patient's cardiac function. High-dose Metoprolol can not only notably improve heart function, but also significantly increase LVEF levels, and the incidence of adverse drug reactions is not obvious, which is similar to the results of present study [18-20]. Due to its high fat solubility, Metoprolol can pass through the blood-brain barrier, and its concentration in cerebrospinal fluid is about 70% of the blood concentration, so patients may suffer from headaches, dizziness, fatigue, insomnia, and dreaminess after use. Under the circumstance of high-dose use, palpitations, gastrointestinal reactions (nausea, vomiting), etc. can also occur [21, 22]. The mechanism may be: (1) Nicorandil is a nitrate compound and a potassium channel activator. It has the effect of relaxing two blood vessels. Nicorandil is a derivative of niacinamide with a nitro group in the side chain, which can reduce calcium influx, relax matrix, increase the volume, thereby promoting myocardial respiration and energy production and simulating ischemic preconditioning to protect cardiomyocytes. (2) Metoprolol belongs to β blockers and has the effects of anti-sympathetic nerve excitation, lowering blood pressure, slowing heart rate, and reducing myocardial oxygen consumption [6, 7]. The sample size involved in this study is small, and the sample size needs to be expanded to draw a more reliable conclusion.

In conclusion, high-dose Metoprolol combined with Nicorandil has a notable effect on the treatment of unstable angina pectoris, which can remarkably reduce the frequency and duration of angina attacks, improve the patient's heart function, quality of life and body function, with smaller adverse reactions and high clinical value.

## Disclosure of conflict of interest

None.

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