Am J Transl Res 2021;13(7):7906-7913
www.ajtr.org /ISSN:1943-8141/AJTR0132040

Original Article

Metoprolol combined with nicorandil on unstable angina pectoris can reduce incidence of cardiovascular events and inflammatory reactions

Junhua Zhang, Zhi Xin

Second Department of Cardiology, Laixi City People's Hospital, Laixi 266600, Qingdao, Shandong Province, China

Received February 18, 2021; Accepted April 12, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Objective: This research was designed to investigate the efficacy of metoprolol combined with nicorandil on unstable angina pectoris (UAP). Methods: Totally 174 UAP patients treated in the Laixi City People's Hospital from May 2017 to December 2019 were taken as the research objects. They were divided into the control (n=79, CG) and joint (n=95) groups (JG). Patients in the CG were treated with metoprolol, while those in the JG were treated with nicorandil. The clinical efficacy, adverse events and inflammatory reactions were observed. Results: The effective rate of the JG was better than that of the CG after treatment. There were no additional adverse reactions, and the incidence of cardiovascular events reduced. The changes of cardiac function manifested that the left ventricular end systolic diameter (LVESD) and left ventricular end diastolic diameter (LVEDD) in the JG were lower than those in the CG, while the left ventricular ejection fraction (LVEF) was higher. In addition, the serum levels of total cholesterol (TC), triglyceride (TG), high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) in the JG were lower than those in the CG. Conclusion: Metoprolol combined with nicorandil is effective for UAP patients, which reduces the incidence of cardiovascular adverse events and inhibits inflammatory reactions.

Keywords: Unstable angina pectoris, metoprolol, nicorandil

Introduction

Angina pectoris (AP) is a kind of cardiovascular disease characterized by chest pain, which can be divided into stable angina pectoris (SAP) and unstable angina pectoris (UAP) [1]. UAP is mainly caused by the secondary lesion of coronary plaque rupture and erosion and the decrease of local myocardial blood flow [2]. Although the mortality of UAP has decreased year by year in the past few years, the prevalence rate is still high (5.7% for men and 6.7% for women). Thus, it's still a major public health problem [3]. UAP mainly lasts for a long time at rest or at night. Because of its special physiological mechanism and clinical manifestations, it may develop into acute myocardial infarction or sudden death if it's not treated in time [4].

In the past decades, due to the progress of treatment selection and drug development, the scheme of UAP has made great progress [5]. Metoprolol is a common therapeutic drug, which can reduce the production of adrenalin, adjust the sympathetic excitability of patients, improve the compliance of myocardium and effectively relieve myocardial injury [6]. Nicorandil is also a familiar anti-angina drug, which can promote the blood flow of coronary artery, relieve coronary spasm, dilate arterial blood vessels, and protect the heart positively [7]. Savonitto *et al.* reported that metoprolol had short-term beneficial effects in UAP patients who had not been treated with β blockers, but the combination with nifedipine fixation could not further increase the benefits [8]. The evidence suggests that compared with placebo, the cardiovascular events of SAP patients treated with nicorandil are moderately reduced, but this prognostic benefit has not been confirmed [9]. Although metoprolol and nicorandil alone are commonly used in AP patients [10, 11], there are few reports on their combined use.

In terms of pathophysiology of UAP, inflammatory mediators play a key role in coronary artery inflammation, and higher inflammatory markers are related to patients' severity and poor car-

diovascular prognosis [12]. This research mainly assessed the efficacy of metoprolol combined with nicorandil on UAP, and its influence on the incidence of cardiovascular events and inflammatory reactions.

Materials and methods

Totally 174 UAP patients who admitted to the Laixi City People's Hospital from May 2017 to December 2019 were regarded as the research objects. This experiment was ratified by the Ethics Committee, and informed consent forms were signed. Inclusion criteria were as follows: It met the diagnostic criteria of UAP in the Guidelines for the Management of Unstable Angina Pectoris Patients/Non-ST-Segment Elevation Myocardial Infarction (UAP/NSTEMI) [13]; course of disease >1 month; not over 80 years old; complete clinical data. Exclusion criteria were as follows: those had a cardiothoracic surgery history; those who were allergic to drugs in this test; patients with mental disorders, heart, liver and kidney dysfunction, malignancies, congenital heart disease and coagulation dysfunction.

Therapeutic methods

After being admitted to hospital, all patients received continuous mask oxygen inhalation, ECG monitoring, anticoagulation, lipid regulation and other routine treatments. Aspirin (Hunan Xinhui Pharmaceutical Co., Ltd., China, H43021756) was taken orally, 100 mg/time, once daily. Isosorbide dinitrate (Shandong Boshan Pharmaceutical Co., Ltd., China, H3702-2795) was taken orally, 60 mg/time, once daily. Low molecular weight heparin sodium (ALFA WASSERMANN S.p.A, H20140281, Italy) was injected, 4200 U/time, once/12 h. Totally 174 patients were divided into control group (CG) (n=79) and joint group (JG) (n=95). All patients in the CG were treated with metoprolol (Yantai Juxian Pharmaceutical Co., Ltd., China, H201-43225). It was 12.5 mg/once, 2 times/day, and then gradually increased to 25 mg. On this basis, the JG was given nicorandil (Xi'an Hanfeng Pharmaceutical Co., Ltd., China, H61-022860), 5 mg/time, 3 times/day. All patients were treated continuously for 1 month.

Outcome measures

Clinical efficacy: markedly effective: The signs returned to normal, the symptoms of angina basically disappeared, and there was no cardiovascular events; effective: The incidence of AP was obviously less, and ST-T of ECG tended to be normal; ineffective: The symptoms of AP was not relieved or even aggravated. (Markedly effective cases+effective cases)/total cases × 100% = total effective rate.

Adverse reactions including dizziness, headache and fatigue during treatment were observed, and cardiovascular adverse events such as myocardial infarction, recurrent chest pain and recurrent AP were recorded. The serum total cholesterol (TC) and triglyceride (TG) levels of patients were measured by BS-280 automatic biochemical analyzer (Shenzhen Mindray Biomedical Electronics Co., Ltd., China). The cardiac function indexes were observed before and after treatment, including left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF). The high-sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels in serum were tested via enzyme-linked immunosorbent assay (ELISA) [14]. The kit was provided by Shanghai Zhenyu Biotechnology Co., Ltd., China (CSB-E08617h-1, CSB-E16524h-1). Those levels were tested by Varioskan LUX multi-functional strip reader (ThermoFisher Scientific, Shanghai, China) and operated strictly in light of the instructions.

Statistical analysis

The data were analyzed via SPSS 26.0 (Beijing Strong-vinda Information Technology Co., Ltd., China), and the pictures were drawn by Graphpad Prism 6.0. $P<0.05$ denoted that the difference was statistically remarkable. The counting data, represented as (%), were compared by Chi-square test and marked by χ^2. The measurement data were marked as mean ± SEM and compared through t-test or paired-t test.

Results

General data

We collected general data of two groups of patients. Statistical analysis manifested that there was no marked difference in clinical data such as course of disease, age, complications and risk degree between both groups. Sinus bradycardia, prolonged QT and extensive abnormality of ST-T wave can be seen in UA patients ($P>0.05$) (**Table 1**; **Figure 1**).

Table 1. General data of patients

Category	Joint group (n=95)	Control group (n=79)	t/χ^2	P
Course of disease (d)	2.71±0.28	2.76±0.31		
Gender			0.112	0.738
Man	59 (62.11)	51 (64.56)		
Woman	36 (37.89)	28 (35.44)		
Age	61.59±4.06	60.48±4.16		
Complicated with hypertension			0.034	0.854
Yes	24 (25.26)	19 (24.05)		
No	71 (74.74)	60 (75.95)		
Complicated with diabetes			0.247	0.619
Yes	21 (22.11)	20 (25.32)		
No	74 (77.89)	59 (74.68)		
Complicated with hyperlipidemia			0.043	0.836
Yes	43 (45.26)	37 (46.84)		
No	52 (54.74)	42 (53.16)		
Risk degree			4.092	0.129
Low risk	36 (37.89)	31 (39.24)		
Moderate risk	39 (41.05)	40 (50.63)		
High risk	20 (21.05)	8 (10.13)		
Disease type			1.172	0.557
Initial exertional angina pectoris	29 (30.53)	20 (25.32)		
Deteriorating exertional angina pectoris	18 (18.95)	14 (17.72)		
Resting angina pectoris	45 (47.37)	45 (56.96)		
NYHA classification of cardiac function			0.195	0.978
Class I	45 (47.37)	35 (44.30)		
Class II	30 (31.58)	27 (34.18)		
Class III	19 (20.00)	16 (20.25)		
Class IV	1 (1.05)	1 (1.27)		

Changes of blood lipid levels before and after treatment

We observed the changes of blood lipid levels before and after treatment. There was no remarkable difference in TC and TG levels between both groups before treatment ($P>0.05$). While the levels decreased after treatment ($P<0.05$), and those in the JG were lower than those in the CG ($P<0.05$) (**Figure 2**).

Cardiac function of both groups before and after treatment

We observed the cardiac function of two groups of patients before and after treatment. There was no marked difference in LVESD (mm), LVEDD (mm) and LVEF (%) between the two groups ($P>0.05$) before treatment. While LVESD and LVEDD of patients after treatment were lower ($P<0.05$), and LVEF was higher ($P<0.05$). The LVESD and LVEDD of patients in the JG were lower than those in the CG, and the LVEF was higher (both $P<0.05$) (**Figure 3**).

Incidence of adverse reactions in both groups

We observed the adverse reactions of patients during treatment. During the treatment period, there were 3 dizzy cases (3.16%), 5 headache cases (5.26%), 4 tired cases (4.21%) in the JG, and the incidence of adverse reactions was 12.63%. While in the CG, there were 3 cases of vertigo (3.80%), 3 of headache (3.80%), 2 of fatigue (2.53%), and the incidence was 12.63%. The incidence of adverse reactions revealed no obvious difference ($P>0.05$) (**Table 2**).

Clinical efficacy of two groups of patients

We assessed the clinical efficacy of patients after treatment. In the JG, 60 cases (63.16%)

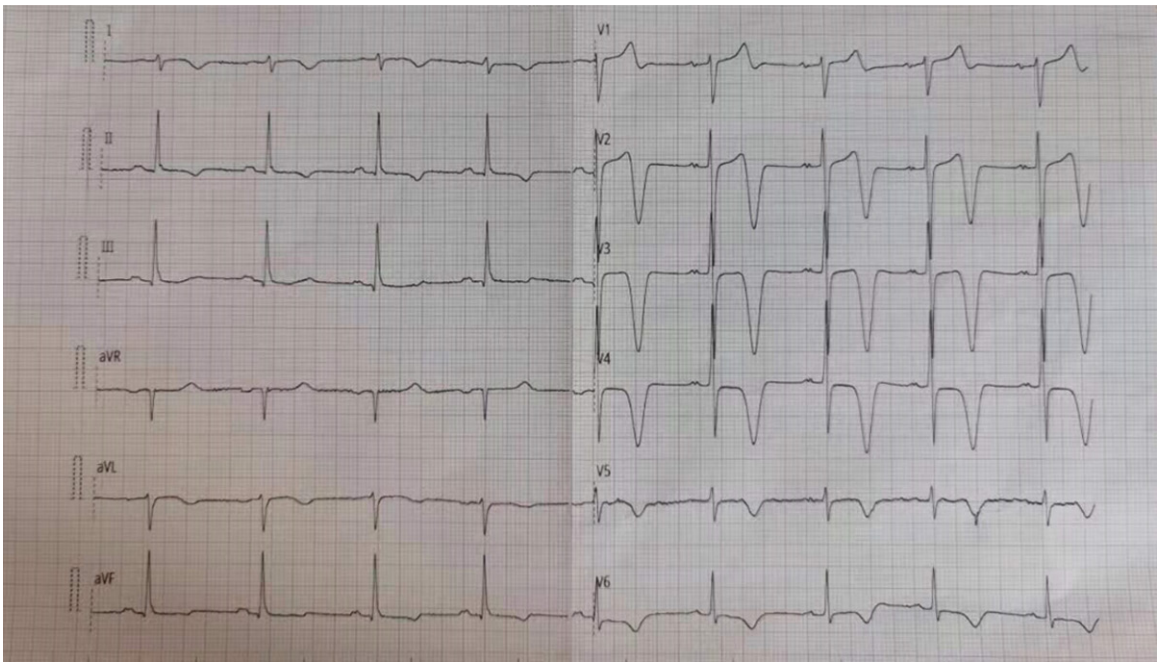

Figure 1. Typical ECG report of UA patients.

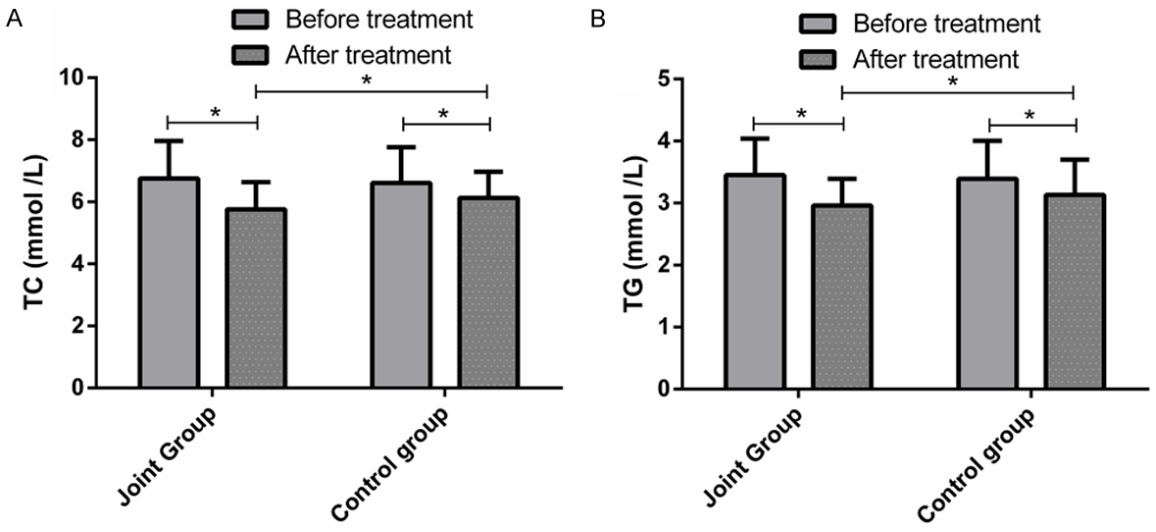

Figure 2. Changes of blood lipid levels before and after treatment in joint group and control group. After treatment, the TC (A) and TG (B) levels of patients in the two groups decrease, and the levels of patients in the joint group are lower than those in the control group. Note: *P<0.05.

were markedly effective, 25 (26.32%) were effective, 10 (10.53%) were ineffective, and the effective rate was 89.47%. While in the CG, 34 cases were markedly effective (43.04%), 28 were effective (35.44%), 17 were ineffective (21.52%), and the rate was 78.48%. The rate of the JG was better than that of the CG (P<0.05) (**Table 3**).

Incidence of cardiovascular events of patients in both groups

We observed the occurrence of cardiovascular events in patients. After treatment, there was 1 case (1.05%) suffered from recurrent chest pain, 2 cases (2.11%) suffered from recurrent angina pectoris in the JG, and the incidence of

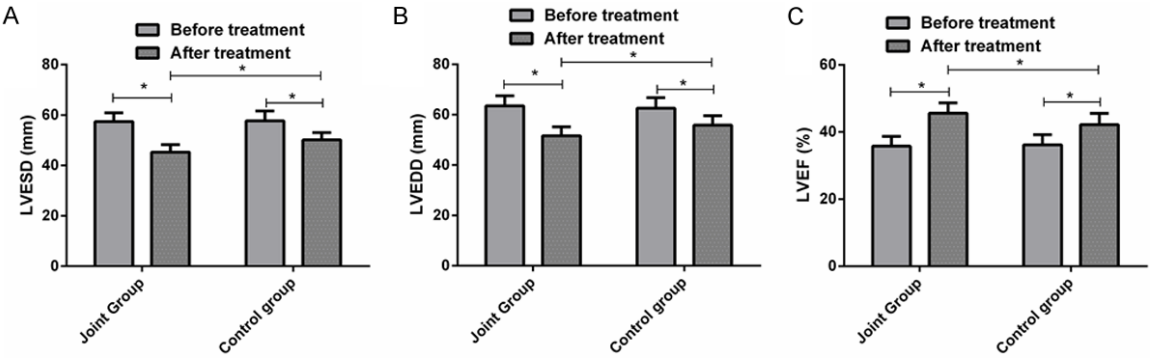

Figure 3. Changes of cardiac function before and after treatment in joint group and control group. Compared with the control group, LVESD (A) and LVEDD (B) in the joint group are lower and LVEF (C) is higher after treatment. Note: *P<0.05.

Table 2. Incidence of adverse reactions in joint group and control group

Cardiovascular events	Joint group (n=95)	Control group (n=79)	t/χ^2	P
Vertigo	3 (3.16)	3 (3.80)	0.053	0.818
Headache	5 (5.26)	3 (3.80)	0.211	0.646
Tired	4 (4.21)	2 (2.53)	0.365	0.546
Total incidence efficiency (%)	12.63	10.13	0.266	0.606

Table 3. Comparison of clinical efficacy between joint group and control group

Clinical efficacy	Joint group (n=95)	Control group (n=79)	t/χ^2	P
Markedly effective	60 (63.16)	34 (43.04)		
Effective	25 (26.32)	28 (35.44)		
Ineffective	10 (10.53)	17 (21.52)		
Effective rate (%)	89.47	78.48	3.976	0.046

Table 4. Incidence of cardiovascular events in patients of joint group and control group

Cardiovascular events	Joint group (n=95)	Control group (n=79)	t/χ^2	P
Myocardial infarction	0 (0.00)	2 (2.53)	2.433	0.119
Recurrent chest pain	1 (1.05)	4 (5.06)	2.486	0.115
Recurrent angina pectoris	2 (2.11)	5 (6.33)	1.993	0.158
Total incidence efficiency (%)	3.16	13.92	6.757	0.009

cardiovascular events was 3.16%. While in the CG, there were 2 cases of myocardial infarction (2.53%), 4 of recurrent chest pain (5.06%), 5 of recurrent angina pectoris (6.33%), and the incidence was 13.92%. The incidence in the JG was lower than that in the CG (P<0.05) (**Table 4**).

Inflammatory reactions before and after treatment in both groups

We observed the inflammatory reactions of two groups of patients before and after treatment. There was no marked difference in serum levels of hs-CRP and IL-6 between the JG and the CG before treatment (P>0.05). While the levels decreased after treatment (P<0.05), and those in the JG were lower than those in the CG (P<0.05) (**Figure 4**).

Discussion

Clinically, UAP often presents recurrent AP, which will seriously damage patients' physical and mental health [15]. In this research, we used metoprolol combined with nicorandil to treat UAP patients, and found that the combined use of the two drugs had better clinical efficacy and could reduce the incidence of cardiovascular events and inflammatory reactions.

The main change is atherosclerosis, which is usually relevant to abnormal changes of blood lipids [16]. Nowadays, it's usually treated by antiplatelet, hypolipidemic drugs, and nitrates [17]. Metoprolol, a β-blocker drug, can influence theaphenolamine mediation, thereby inhibiting myocardial remodeling and slowing down

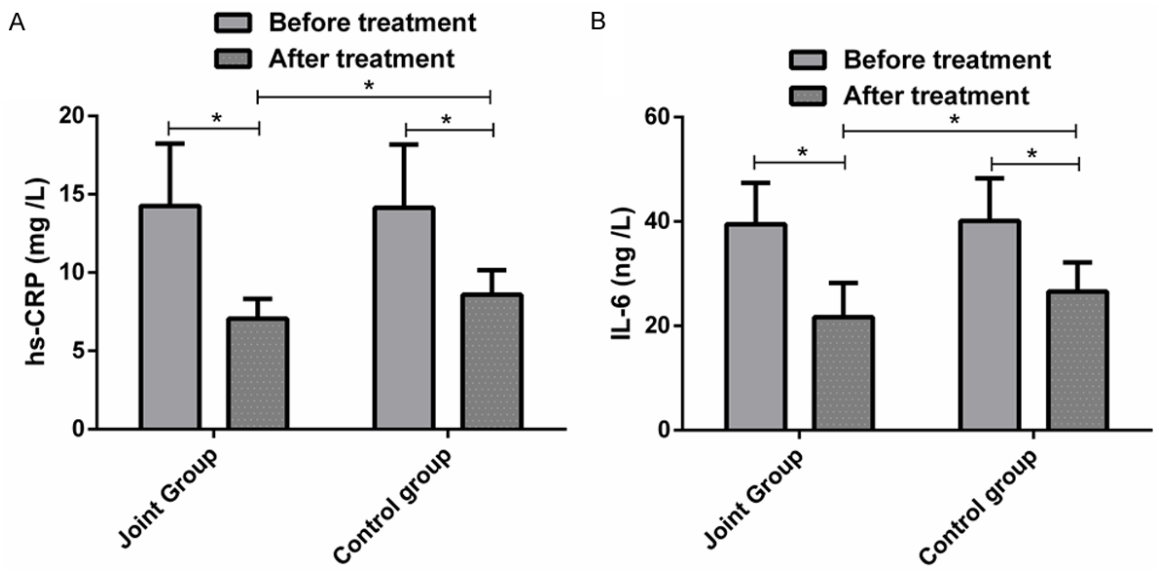

Figure 4. Changes of inflammatory factors before and after treatment in joint group and control group. After treatment, the levels of serum hs-CRP and IL-6 in the two groups decrease, and the levels in the joint group are lower than those in the control group. Note: *P<0.05.

myocardial injury in patients [18]. Nicorandil is an ATP-sensitive potassium channel opener, which mainly acts on smooth muscle and can inhibit the effect of ischemia-reperfusion and improve cardiac function [19]. In our research, metoprolol combined with nicorandil can improve blood lipid level, cardiac function and clinical efficacy of UAP patients. Similarly, Pizarro *et al.* reported that early application of metoprolol before reperfusion in patients with acute myocardial infarction could protect their cardiac function [20]. In addition, Wang *et al.* has shown that the infusion of nicorandil could reduce QTd and Tp-e interval in UAP patients [21]. It has also been reported that compared with placebo, nicorandil can reduce transient myocardial ischemia, non-persistent ventricular arrhythmia and supraventricular arrhythmia on the basis of active anti-angina treatment, without increasing additional adverse events [22]. In our report, the combined use of the two drugs will not increase the adverse reactions, but can reduce the incidence of cardiovascular events, with high safety.

Research has shown that inflammation plays a vital role in the pathogenesis of UAP patients [23]. UAP is characterized by elevated levels of fibrinogen, serum amyloid, CRP and IL-6 (the main inducement of CRP production in liver) in acute phase, which is relevant to poor short-term and long-term prognosis of patients [24]. Zaremba *et al.* discovered that some pro-inflammatory cytokines such as IL-1β, IL-6, IL-17, TNF-α and CRP and fibrinogen in the serum of UAP increased [25]. Therefore, it may be one of the feasible therapeutic mechanisms of UAP through the continuous inflammatory reaction. Our research demonstrates that metoprolol combined with nicorandil can reduce inflammatory reaction in UAP patients. So, these two drugs have anti-inflammatory effects. This may be because metoprolol can effectively reduce cardiac conduction autonomy and myocardial oxygen consumption, while nicorandil can relieve coronary spasm and promote coronary blood flow, which can reduce myocardial injury and inhibit inflammatory reactions [26, 27]. Although our research suggests that metoprolol combined with nicorandil is beneficial to UAP patients. Nevertheless, there are still some shortcomings as patients' quality of life was not recorded, and that the anti-inflammatory mechanisms of the two drugs still need further investigation.

To sum up, the use of metoprolol combined with nicorandil on UAP patients has good clinical effect. It can reduce the incidence of cardiovascular adverse events and inhibit inflammatory reactions, with good safety.

Disclosure of conflict of interest

None.

Address correspondence to: Junhua Zhang, Second Department of Cardiology, Laixi City People's Hospital, NO. 69 Yantai Road, Laixi 266600, Qingdao, Shandong Province, China. Tel: +86-0532-8187-9959; E-mail: 15966893267@163.com

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