Int J Clin Exp Med 2018;11(7):6993-6998
www.ijcem.com /ISSN:1940-5901/IJCEM0075870

Original Article

Therapeutic effect and safety of nicorandil in treatment of refractory angina pectoris

Ya Li, Yongxing Liu, Wanzhong Peng, Bingxun Wang, Tao Geng, Zesheng Xu

Department of Cardiovascular Medicine, Cangzhou Central Hospital, Cangzhou City 061000, Hebei Province, P. R. China

Received March 12, 2018; Accepted April 25, 2018; Epub July 15, 2018; Published July 30, 2018

Abstract: Objective: To investigate the therapeutic effect and adverse reactions to nicorandil in patients with refractory angina pectoris (AP). Methods: Between March 2014 and December 2016, a total of 70 patients with refractory AP admitted to Cangzhou Central Hospital were recruited in this study and subdivided into the experiment group (n=35) and the control group (n=35) by means of a random number table. The patients in the control group were assigned to receive placebo in addition to basic care, while those in the experiment group were assigned to receive nicorandil in addition to basic care. One month after treatment, the therapeutic effects, frequency and duration of AP, the changes in ST-T segment EEG, and adverse reactions of the patients were compared between the two study groups. Results: The response rate of the experiment group was remarkably higher than that of the control group (94.3% vs 77.1%, P=0.035); greater improvements in the duration (P=0.034) and frequency (P=0.004) of refractory AP were observed in the experiment group. The improvement rate of ECG in the experiment group after treatment was significantly higher than that of the control group (91.4% vs 71.4%, P=0.028). However, the rates of overall adverse reactions were generally similar in both groups (P=0.167). Conclusion: Nicorandil was effective in treating refractory AP, resulting in great improvements in the frequency and duration of refractory AP, ST-T segment of ECG, and adverse reactions. Therefore, it is a potent agent for the treatment of refractory AP.

Keywords: Nicorandil, refractory angina pectoris, electrocardiogram, clinical efficacy

Introduction

With the improvement of people's life and changes in daily diets, the prevalence of cardiovascular diseases is rising on a yearly basis. Refractory angina pectoris (AP) is a clinically common disorder involving the cardiovascular system. It is characteristic of a long course of disease, great harm and difficulty in treatment, and poses a serious threat to the patients' life and health [1-3]. Therefore, how to treat refractory AP and alleviate clinical symptoms effectively is a problem encountered by clinicians [4].

The principle for management of AP is to improve the blood supply in the myocardia and reduce oxygen consumption [5]. Nicorandil, a nitrate compound and an ATP-sensitive potassium channel opener, activates intracellular guanylate cyclase, resulting in reduced content of intracellular calcium, elevated cGMP levels, and vasodilation [6, 7]. Studies show that nicorandil relieves spasm of the coronary artery and dilates coronary arteries to improve coronary blood flow and myocardial blood supply, while protecting the myocardia and improving cardiac function without affecting blood pressure, heart rate or conduction [8, 9]. Overall, previous studies have primarily focused on exploring nicorandil in the treatment of stable AP [10, 11]. However, the effect of nicorandil on refractory AP remains unknown. Therefore, the current study was designed to delve into the efficacy and safety of nicorandil use in refractory AP.

Materials and methods

Patients

From March 2014 to December 2016, 70 patients with confirmed refractory AP admitted to Cangzhou Central Hospital were enrolled in the current study. Patients older than 18 years were eligible if they met the relevant criteria for

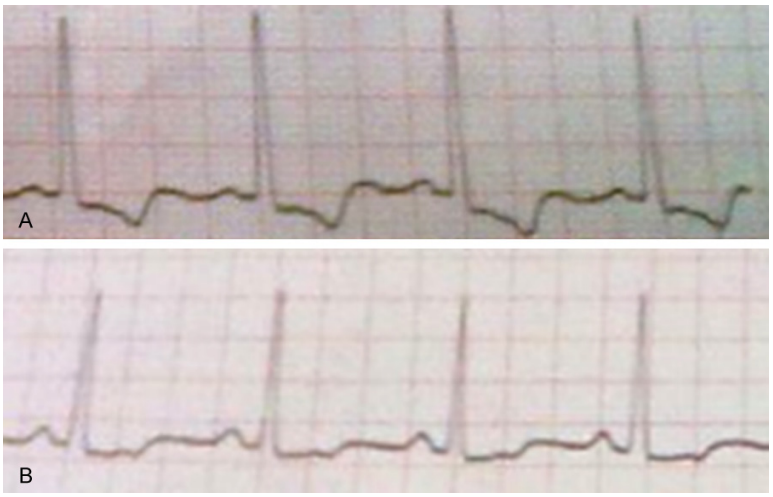

Figure 1. Improvement in ECG, the inverted T-waves changed to flatness. A: Before surgery; B: After surgery.

diagnosing refractory AP. Eligible patients were also present with objective evidence for myocardial ischemia, and severe angina symptoms. Eligible patients included those that showed previous ineffective medical treatment was not suitable for coronary intervention or coronary artery bypass surgery, or those that had AP symptoms after repeated surgeries or that provided complete clinical data and were able to follow the protocol [7]. Patients were excluded if they had severe hepatic or renal dysfunction, cerebral trauma within half a year before enrollment, aortic stenosis, acute myocardial infarction or other diseases inducing myocardial ischemia alone or combined with conduction block and other arrhythmia, malignant tumor, disturbance of consciousness, or a primary hematological disorder. Eligible patients were assigned to the experiment group (n=35) or the control group (n=35) in terms of a random number table. This study was reviewed and approved by the Ethics Committee of Cangzhou Central Hospital and all the patients and their families provided written informed consent.

Study treatment

All the eligible patients were supplied with basic care, including bedrest, oxygen inhalation, β-receptor blockers for ventricular rate control, aspirin for anticoagulation, Lipitor for lipid lowering and atherosclerotic plaque stability, calcium channel blockers for blood pressure control, and metformin or acarbose for glycemic control. In a double-blind manner, all the patients in the experiment group received oral nicorandil 3 times per day at 5 mg/dose in addition to the basic care, whereas those in the control group were given matching placebo. The study treatment lasted for 1 month.

Outcome measures

Primary outcome was clinical response to treatment of the patients in the experiment group and the control group at 2 weeks after treatment. The two groups were compared in the clinical response to treatment at 2 weeks after treatment. Clinical response to the treatment was defined that the patient had an AP attack of no more than 2 minutes, with a frequency of less than twice per week, or the symptoms disappeared and the patients could conduct daily activities normally or under a mild influence.

Secondary outcomes consisted of the duration and frequency of refractory AP of the two groups at 2 weeks, the improvement in electrocardiogram (ECG), and the adverse events of the two groups at 1 month including dizziness, headache, gastrointestinal disorder, flushing, and hypotension. The values on the ECG returning to normal, the ST-ST-T segment depression back up to greater than 0.05 mV on EGG or the inverted T-wave changing to flatness or uprightness were considered as improved ECG (**Figure 1**).

Statistical analysis

All the statistical data were analyzed with the use of the SPSS software, version 20.0. Count data are expressed as percentages, with the Chi-square tests for between-group comparisons and the paired Chi-square test for comparisons before and after treatment. Measurement data are described as mean ± standard deviation, with the paired t-tests for comparisons before and after treatment and the independent samples t-test for between-group comparisons. $P<0.05$ was set as statistically significant difference.

Table 1. Baseline characteristics of the patients

Variable	Case	Age (year)	M/F (n)	BMI (kg/m^2)	H (n)	DM (n)	HY (n)	DC (year)
EG	35	57.3±5.4	24/11	24.2±1.2	20	9	6	1.5±0.6
CG	35	56.7±4.8	22/13	23.9±1.1	19	10	5	1.3±0.4
t/χ^2		0.144	0.254	0.319	0.058	0.072	0.108	0.362
P		0.893	0.615	0.766	0.810	0.788	0.743	0.731

Note: M denotes male, F female, H hypertension, DM diabetes mellitus, HY hyperlipidemia, DC disease course, EG experiment group, and CG control group.

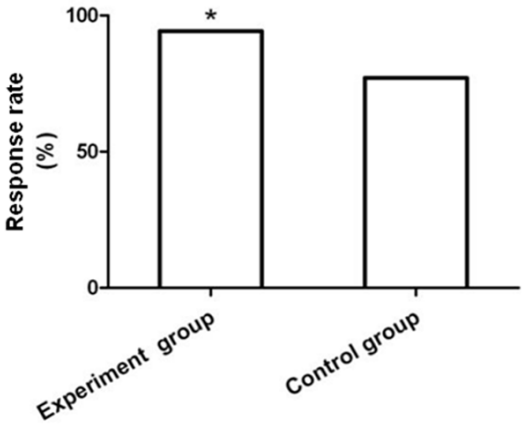

Figure 2. Comparison of clinical response to treatment of the two groups. Compared with the control group, *P<0.05.

Results

Baseline characteristics of the patients

The characteristics of the patients at baseline including age, gender, hypertension, diabetes mellitus and hyperlipidemia were generally well-matched in the two groups, so they were comparable (P>0.05, **Table 1**).

Clinical response

After treatment, 33 patients had clinical responses to treatment and 2 patients had no clinical responses to treatment in the experiment group; 27 patients had clinical responses to treatment and 8 patients had no clinical responses to treatment in the control group. The response rates differed substantially between the two groups (94.3% vs 77.1%, χ^2=4.456, P=0.035), as reported in **Figure 2**.

Duration and frequency of AP

The duration and frequency of AP were largely similar between the two study groups before treatment (Both P>0.05), nevertheless they were strikingly improved in both groups after treatment (Both P<0.05), with more favorable duration and frequency of AP in the experiment group after treatment (Both P<0.05; **Table 2**).

EEG improvements

Improved EEGs after treatment were reported in 32 patients in the experiment group, and no improved EEGs in 3 patients. By contrast, improved EEGs after treatment occurred in 25 patients in the control group, and no improved EEGs in 10 patients. The profile of improved EEGs after treatment were remarkably different between the two groups (91.4% vs 71.4%, χ^2=4.838, P=0.028; **Figure 3**).

Adverse reactions of patients

The rates of dizziness, headache, gastrointestinal reactions, flushing, and hypotension differed insignificantly in the two groups during the treatment period (All P>0.05); the rate of overall adverse reactions in the experiment group was only slightly higher than that of the control group (20% vs 8.6%, χ^2=1.913, P=0.167), as shown in **Table 3** and **Figure 4**.

Discussion

Refractory AP is a spectrum of clinical syndromes which are caused by myocardial anoxia as a result of an imbalance between oxygen need and supply in the myocardia. Without timely and effective treatment, the patients with refractory AP may develop acute myocardial infarction, sudden cardiac death, and other adverse cardiac events [12, 13]. Although the current routine agents which include β-receptor blockers, nitrates and statins dilate coronary vessels, reduce myocardial oxygen consumption, diminish myocardial contractility, and exert a cardio-protective effect, the agents are associated with poor clinical response and

Table 2. Duration and frequency of AP attack of the patients

Variable	Control group	Experiment group	t value	*P* value
Case	35	35		
Duration (min/episode)				
Before treatment	7.3±2.1	6.9±1.9	0.245	0.819
After treatment	5.7±1.3	2.9±0.8	3.177	0.034
t value	2.468	3.361		
P value	0.021	0.028		
Frequency (episode/week)				
Before treatment	15.1±3.3	14.6±2.9	0.197	0.853
After treatment	10.8±2.4	2.5±0.6	5.811	0.004
t value	2.886	7.077		
P value	0.016	0.002		

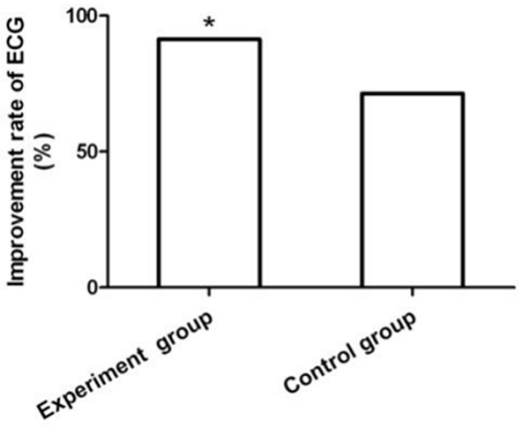

Figure 3. Comparison of EEG improvements after treatment between the two groups. Compared with the control group, *P<0.05.

prognosis in patients with refractory AP. Therefore, it is of great value and practical implication to find effective regimens for refractory AP.

Nicorandil, a novel vasodilator, acts in potassium channel regulation and calcium channel intermittently blocking to dilate coronary arteries, especially small coronary ones, hence alleviating the symptoms of AP [14]. Studies demonstrate that nicorandil functions similarly as nitrates to dilate coronary arteries and promote venous regurgitation [15, 16]. Nicorandil also effectively precludes myocardial ischemia-associated severe arrhythmia, decreases the incidence of adverse cardiac events, and improves the prognosis in patients [17, 18]. A previous animal experiment revealed that by activating opioids, nicorandil use resulted in effective pain relief in mice and improvement in medication compliance [19]. Therefore, nicorandil not only dilates coronary arteries, but also exerts an analgesic effect, alleviating the symptoms of angina.

However, few reports have focused on the clinical response to nicorandil in patients with refractory AP. In the current study, the results indicated that the response rate was 94.3% with nicorandil, significantly higher than that with placebo. The duration and frequency of AP in the experiment group were more substantially improved as composed with those in the control group. In terms of the ECG profile, the improvement rate of EEGs in the experiment group was 91.4%, which was strikingly higher than that in the control group. Nicorandil resulted in great improvements in the symptoms and ECG of patients with refractory AP. This might be due to the fact that nicorandil effectively improves cardiac blood supply, reduces cardiac load, and improves myocardial ischemia preconditioning and the metabolism of energy metabolism to protect the myocardia. Moreover, nicorandil use is also associated with improved fibrinolysis in the body, reduced or resolved coronary thrombosis, as well as a lower rate of adverse events including myocardial infarction [20].

As far as adverse reactions are concerned, the results of the current study demonstrated that the rate of overall adverse reactions in the experiment group was 20%, insignificantly higher than that in the control group. This suggests that nicorandil medication for refractory AP results in lower adverse reactions in patients, which might be explained by the fact that nicorandil opens mitochondrial sensitive potassium-channels and reduces oxidative stress-induced nuclear morphological changes in cells and inhibits cellular proliferation and apoptosis. Another study reported that nicorandil use was associated with improved activity tolerance, fewer adverse events which include dizziness, headache, and gastrointestinal reactions, which were consistent with the results reported in our current study [21].

Table 3. Adverse events of patients in the two groups (n)

Variable	Case (n)	Dizziness, headache	Gastrointestinal reaction	Flushing	Hypotension
EG	35	3	1	1	2
CG	35	1	0	1	1
χ^2		1.107	1.401	0.000	0.355
P value		0.293	0.237	1.000	0.551

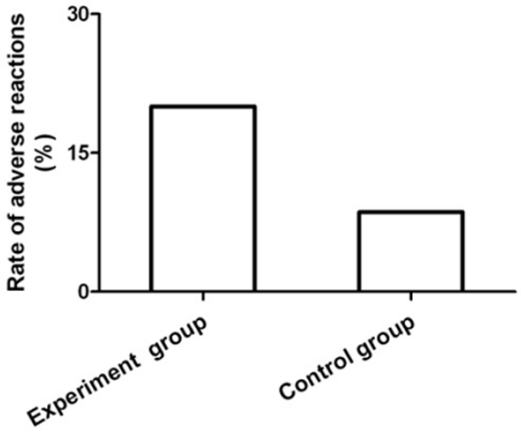

Figure 4. Rates of overall adverse reactions to treatment of patients in the two groups.

In conclusion, nicorandil, an ATP-sensitive K + channel activator, significantly improved myocardial blood supply and the EEG profiles, and greatly alleviated the symptoms of patients with refractory AP. Therefore, Nicorandil is a safe and potent agent in the treatment of refractory AP. The results of the current study can bring some insights into clinical medication for the disease. Nevertheless, the exact mechanisms of nicorandil in the management of refractory AP remains unclear, which should be clarified in further studies.

However, there are still some limitations in the current study, such as a small sample size, inevitable confounding factors, and a single center study. Therefore, additional multi-center randomized trials with large samples are needed for further validation.

Disclosure of conflict of interest

None.

Address correspondence to: Zesheng Xu, Department of Cardiovascular Medicine, Cangzhou Central Hospital, No.16, Xinhua West Road, Canal District, Cangzhou City 061000, Hebei Province, P. R. China. Tel: +86-0317-2075744; E-mail: zeshengxu35@163.com

References

[1] Poppi NT, Gowdak LH, Dourado LO, Adam EL, Leite TN, Mioto BM, Krieger JE, Cesar LA and Pereira AC. A prospective study of patients with refractory angina: outcomes and the role of high-sensitivity troponin T. Clin Cardiol 2017; 40: 11-17.

[2] Mischie A, Chanseaume S, Gaspard P, Andrei CL, Sinescu C and Schiariti M. Oral sirolimus: a possible treatment for refractory angina pectoris in the elderly. Int J Cardiol 2016; 222: 1097-1104.

[3] Sainsbury PA, Fisher M and de Silva R. Alternative interventions for refractory angina. Heart 2017; 103: 1911-1922.

[4] Waltenberger J. Chronic refractory angina pectoris: recent progress and remaining challenges. Eur Heart J 2017; 38: 2556-2558.

[5] Dobias M, Michalek P, Neuzil P, Stritesky M and Johnston P. Interventional treatment of pain in refractory angina. A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2014; 158: 518-527.

[6] Tarkin JM and Kaski JC. Vasodilator therapy: nitrates and nicorandil. Cardiovasc Drugs Ther 2016; 30: 367-378.

[7] Wei J, Watanabe Y, Takeuchi K, Yamashita K, Tashiro M, Kita S, Iwamoto T, Watanabe H and Kimura J. Nicorandil stimulates a Na(+)/Ca(2)(+) exchanger by activating guanylate cyclase in guinea pig cardiac myocytes. Pflugers Arch 2016; 468: 693-703.

[8] Katoh M, Takeda N, Arimoto T, Abe H, Oda K, Osuga Y, Fujii T and Komuro I. Bevacizumab-related microvascular angina and its management with nicorandil. Int Heart J 2017; 58: 803-805.

[9] Wu H, Ye M, Yang J, Ding J, Yang J, Dong W and Wang X. Nicorandil protects the heart from ischemia/reperfusion injury by attenuating endoplasmic reticulum response-induced apoptosis through PI3K/Akt signaling pathway. Cell Physiol Biochem 2015; 35: 2320-2332.

[10] Suleimani HF, Eshraghi A, Daloee MH, Hoseini S and Nakhaee N. Effect of nicorandil on QT dispersion in patients with stable angina pectoris undergoing elective angioplasty: a triple-blind, randomized, placebo-controlled study. Electron Physician 2017; 9: 4934-4941.

[11] Jiang J, Li Y, Zhou Y, Li X, Li H, Tang B, Dai X, Ma T, Li L and Huo Y. Oral nicorandil reduces ischemic attacks in patients with stable angina: a prospective, multicenter, open-label, randomized, controlled study. Int J Cardiol 2016; 224: 183-187.

[12] Abawi M, Nijhoff F, Stella PR, Voskuil M, Benedetto D, Doevendans PA and Agostoni P. Safety and efficacy of a device to narrow the coronary sinus for the treatment of refractory angina: a single-centre real-world experience. Neth Heart J 2016; 24: 544-551.

[13] Giannopoulos AA, Giannoglou GD and Chatzizisis YS. Pharmacological approaches of refractory angina. Pharmacol Ther 2016; 163: 118-131.

[14] Chow C, Cardona M, Raju PK, Iyengar S, Sukumar A, Raju R, Colman S, Madhav P, Raju R, Reddy KS, Celermajer D and Neal B. Cardiovascular disease and risk factors among 345 adults in rural India-the Andhra Pradesh rural health initiative. Int J Cardiol 2007; 116: 180-185.

[15] Hirohata A, Yamamoto K, Hirose E, Kobayashi Y, Takafuji H, Sano F, Matsumoto K, Ohara M, Yoshioka R, Takinami H and Ohe T. Nicorandil prevents microvascular dysfunction resulting from PCI in patients with stable angina pectoris: a randomised study. EuroIntervention 2014; 9: 1050-1056.

[16] Padala SK, Lavelle MP, Sidhu MS, Cabral KP, Morrone D, Boden WE and Toth PP. Antianginal therapy for stable ischemic heart disease: a contemporary review. J Cardiovasc Pharmacol Ther 2017; 22: 499-510.

[17] Ishii H, Ichimiya S, Kanashiro M, Amano T, Matsubara T and Murohara T. Effects of intravenous nicorandil before reperfusion for acute myocardial infarction in patients with stress hyperglycemia. Diabetes Care 2006; 29: 202-206.

[18] Yang J, Zhang J, Cui W, Liu F, Xie R, Yang X, Gu G, Zheng H, Lu J, Yang X, Zhang G, Wang Q and Geng X. Cardioprotective effects of single oral dose of nicorandil before selective percutaneous coronary intervention. Anatol J Cardiol 2015; 15: 125-131.

[19] Dutra MM, Nascimento Junior EB, Godin AM, Brito AM, Melo IS, Augusto PS, Rodrigues FF, Araujo DP, de Fatima A, Coelho MM and Machado RR. Opioid pathways activation mediates the activity of nicorandil in experimental models of nociceptive and inflammatory pain. Eur J Pharmacol 2015; 768: 160-164.

[20] Yang EH, Barsness GW, Gersh BJ, Chandrasekaran K and Lerman A. Current and future treatment strategies for refractory angina. Mayo Clin Proc 2004; 79: 1284-1292.

[21] Ye Z, Su Q and Li L. The clinical effect of nicorandil on perioperative myocardial protection in patients undergoing elective PCI: a systematic review and meta-analysis. Sci Rep 2017; 7: 45117.