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Oral nicorandil reduces ischemic attacks in patients with stable angina: A prospective, multicenter, open-label, randomized, controlled study

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ABSTRACT

Objective: To evaluate the efficacy and safety of oral nicorandil in coronary heart disease (CHD) patients with stable angina.
Method: Eligible patients were randomized 1:1 to the nicorandil or control group. Current standard antianginal treatment was continued in both groups, while the patients in the nicorandil group received an additional 12-week treatment of nicorandil (5 mg thrice daily). Primary endpoint was the number of myocardial ischemia measured by 24 h Holter after 12-week treatment. Secondary endpoints included various 24 h Holter indicators, angina occurrence, 6-min walking test (6MWT), ECG QT dispersion (QTd), safety and compliance. Clinical trial registration: NCT01396395.
Results: A total of 402 adult patients with stable angina were enrolled. Two hundred patients were randomized to standard therapy plus nicorandil and 202 patients to standard therapy only. The baseline characteristics of the two groups were comparable. The number of myocardial ischemia attacks after treatment was significantly lower in the nicorandil group (LSMEANS 0.896) than the control group (LSMEANS 1.782), with an adjusted ratio of 0.503 (95% CI: 0.301, 0.840; $P = 0.0086$). No significant differences in total myocardial ischemic burden, maximum ST-depression, longest duration of ST-depression, 6MWT, or heart rate variability were noted between the two groups. Twenty three (11.7%) of nicorandil group and 13 (6.3%) patients of control group reported at least one treatment emergent adverse event, respectively.
Conclusion: Nicorandil significantly reduced the number of ischemic attacks when added to standard antianginal treatment in CHD patients with stable angina. It was well tolerated with no new safety signal identified.

1. Introduction

Chronic stable angina is the most frequent manifestation of stable coronary artery disease (CAD), which is the leading cause of death worldwide [1,2]. In China, CHD has become increasingly prevalent with a projected increase in cardiovascular disease events by 50% between 2010 and 2030 [3]. According to guidelines published by the health authorities of the US (ACC/AHA), Europe (ESC) and China (CSC/CMA), the main aims of the pharmacological management of stable angina are to prevent myocardial infarction and death, reduce the symptoms of ischemic attack and improve quality of life [4–6]. The current treatment for chronic stable angina relies on the use of anti-ischemic drugs that affect hemodynamic state and reduce myocardial oxygen consumption, such as nitrates, β-blockers and calcium channel blockers, and is often combined with secondary prevention measures such as lipid lowering agents and anti-platelet aggregation medicine [7]. However the efficacies of these drugs in Chinese patients have not been established by well-designed clinical trials. Nicorandil (N-[2-hydroxyethyl] nicotinamide nitrate) is an antianginal agent with a dual mechanism of action [8,9]. The action of nicorandil on nitrate-mediated channels causes vasodilation of systemic veins and epicardial coronary arteries; whereas the opening of ATP-sensitive potassium channels in response to nicorandil causes vasodilation of peripheral and coronary resistance arterioles, dilating resistance vessels [10]. The antianginal activity of nicorandil has been reported in many studies

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[8,9,11–17] and its effects in reducing cardiovascular mortality and coronary heart disease (CHD) related symptoms were also clinically manifested [14,18].

Currently, nicorandil is commonly used as a second-line therapy for the treatment of stable angina in areas such as Europe, Japan, South Korea, Taiwan and China. Despite the wide use of nicorandil in China, there was only one Phase III study evaluated nicorandil in Chinese patients with stable angina. The study demonstrated significant reduction in angina attacks and NTG consumption with improved exercise tolerance in patients treated with nicorandil [19]. Nevertheless, the use of secondary prevention medicine for stable angina was less prevalent during the time this study was conducted (2003–2005) than in the current standard of care. In the last decade, standard treatment, especially secondary prevention of coronary heart disease has been tremendously advanced in China. With the management of coronary heart disease in China has become increasingly standardized, whether nicorandil could add substantial clinical benefit to current standard therapies need to be further investigated. Therefore, additional evidence of efficacy from randomized controlled trials in Chinese patients, especially those in which nicorandil is administered in conjunction with first-line antianginal therapies, will be of great importance in the understanding and administration of nicorandil in Chinese stable angina patients. Hence, a multicenter, randomized, open label, standard treatment controlled study was performed to evaluate the efficacy, safety and compliance of nicorandil co-administered with standard first-line treatments in Chinese CHD patients with stable angina.

2. Methods

2.1. Patients

Patients ≥ 18 years old were eligible to participate in the study if they had diagnosis of coronary artery disease with stable angina, as documented by at least one of the following: 1) previous diagnosis of myocardial infarction; 2) underwent percutaneous coronary intervention (PCI) and diagnosis of at least one major coronary branch stenosis ≥ 50%; 3) 3 months after coronary revascularization (PCI or coronary-artery bypass grafting [CABG]); 4) typical angina symptoms, exercise tolerance text positive, or computerized tomography (CT) coronary angiography showed at least one major coronary artery branch stenosis ≥ 50% (or moderate to severe stenosis). Patients need to have at least two times of typical symptoms of myocardial ischemia occurring within a week prior to screening. Exclusion criteria included acute coronary syndrome, left main coronary artery disease by PCI and without revascularization therapy, moderate to severe aortic stenosis, hypertrophic obstructive cardiomyopathy, uncontrolled hypertension, congestive heart failure, echocardiographic ejection fraction < 40%, complete left bundle branch block, Wolff–Parkinson–White syndrome (WPW) syndrome, left ventricular hypertrophy with strain, paced rhythm, as well as liver and renal impairment. All patients provided written informed consent.

2.2. Study design and procedures

This was a phase IV randomized, open-label, controlled, parallel, multicenter clinical study. Eligible patients were randomized 1:1 to two groups, through stratified randomization using random number table in each study center, to either receive a thrice-daily oral dose of nicorandil (5 mg) added to their current optimal anti-angina treatment for 12 weeks or maintain their current standard treatment. Standard therapies including aspirin, long-acting nitrates, β-blockers, calcium channel blockers (CCB), lipid-lowering statin drugs and angiotensin converting enzyme inhibitors (ACEI) were all allowed in the study. Information of patient characteristics were collected at Baseline visit and patients were instructed to return for clinic visits at 4, 8, and 12 weeks after randomization and treatment initiation. Various safety and efficacy indicators were evaluated at Baseline and in Weeks 4, 8 and 12 of treatment.

The study was designed and conducted in accordance with the requirements of Good Clinical Practice (GCP) and the Declaration of Helsinki. The study protocol was approved by corresponding independent ethics committees (IECs). The study was registered with Clinicaltrials.gov: NCT01396395.

2.3. Study endpoints

The primary endpoint was the total number of myocardial ischemia attacks measured by 24-h Holter from baseline. Centralized Holter monitoring (Model: DMS300-4A) and review (Model: CS12) was conducted before treatment period and after the study completion. Holter analyzer and data analyzer were blinded to patient randomization during data collection and analysis, and were un-blinded after the end of the trial and data analysis. Myocardial ischemia attack was defined as 0.08 s after the J point in ECG or compared with baseline levels, ST-segment with horizontal or downward sloping down ≥ 0.1 mV that last for ≥1 min, and interval ≥ 1 min from another ischemic attack, as one array myocardial ischemia. Secondary endpoints included various 24 h holter indicators(i.e. total myocardial ischemic burden, the maximum decrease and longest duration of ST segment depression, ischemic attacks during 6-min walk (6MW) test, heart rate variability rate, number of onset of arrhythmia), walk distance in 6MW test and ECG QT dispersion. Treatment compliance was evaluated as a function of total administered dose of total scheduled dose. Compliance (%) = (actual total dose/planned total dose) × 100%. Planned total dose was calculated based on the planned treatment time of each patient in the trial. If patient compliance was less than 80% or greater than 120%, then that patient was considered as noncompliant. Safety measurements included adverse events (AE), serious adverse events (SAEs), drug-related AE (DRAE), most frequent treatment emergent adverse events (TEAEs) and laboratory safety evaluations. The classification and severity grading of adverse events in the study was based on the Common Terminology Criteria for Adverse Events (CTCAE) [20].

2.4. Statistical analysis

A sample size of 346 was calculated based on a presumption of an average of 4 episodes of myocardial ischemia in the control group, a 15% reduction of myocardial ischemia attack in the treatment vs. control group and a 5% Type I error rate (bilateral). Considering a dropout rate of 15%, a final sample size of 400 was needed to detect the difference of two groups with a statistical power of 90%.

Full analysis set (FAS), efficacy analysis set (EAS), and per protocol set (PPS) were used for efficacy analysis. Safety set (SS) was used for safety analysis. All randomized patients who received study drug were included in FAS and SS. In efficacy evaluation, analysis was performed according to randomized group. In safety evaluation, analysis was performed according to actual group and patients randomized to test group who didn't receive study drug nicorandil were included in control group.

The effect of treatment on the primary endpoint was estimated with the use of Poisson regression test. Corresponding 95% confidence intervals and P values was calculated for confirmatory analysis (bilateral test probability of $P < 0.05$ indicated statistical significance.). For secondary endpoints, purely exploratory t-test or Wilcoxon rank test were used to perform intragroup comparison between baseline and post-treatment visits; while Pearson chi-square test or Fisher exact probability test were used for intergroup comparison between nicorandil and control treatments. In compliance analysis, compliance (%) was defined as (total administered dose/total scheduled dose) × 100%. A patient would be identified as noncompliant if his/her compliance was less than 80% or greater than 120%.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 402 CHD patients with stable angina were enrolled. All of the 402 randomized and treated patients were included in full analysis set (FAS), including 200 patients in nicorandil group and 202 patients in control group. Among all randomized patients, 335 (83.3%) patients completed the study with 160 (80.0%) in nicorandil group and 175 (86.6%) in control group. Of 200 patients randomized to nicorandil group in safety set (SS), 4 patients were included in control group as they did not receive nicorandil. Among 202 patients randomized to control group in SS, 1 patient was included in nicorandil group as that patient received nicorandil. Therefore, 197 patients in nicorandil group and 205 patients in control group were analyzed in SS (Fig. 1). Baseline characteristics were comparable in age, gender, median body mass, and smoking state between the nicorandil group and the control group, respectively. At the time of enrolment, all the patients in the nicorandil and control group were taking one or more types of standard anti-angina therapies such as ACEI/ARB, β-blocker, aspirin/anti-platelet drug and lipid-lowering drugs. Detailed data of patient characteristics, medications and medical history were summarized in Table 1.

3.2. Efficacy evaluation

The number of myocardial ischemia attacks in 24 h after a 12-week treatment occurred significantly less frequently in the nicorandil group than the control group. The least squares means (LSMEANS) of myocardial ischemia attacks were 0.896 (95%CI: 0.317, 2.536) in the nicorandil group and 1.782 (95%CI: 0.629, 5.046) in the control group (adjusted ratio = 0.503; [95%CI: 0.301, 0.840]; $P = 0.0086$) (Fig. 2). In general, no significant difference was observed between the nicorandil and the