Nicorandil versus Conventional Anti-Anginal Therapy in Patients with Multivessel Coronary Artery Disease

Fariborz Farsad, PharmD,* Majid Maleki, MD, Fereidoun Noohi, MD, Kheirollah Gholami, PharmD,** Maryam Moshkani Farahani, MD***

Abstract

Background- Nicorandil, a novel anti-anginal agent, has been characterized as having potent coronary vasodilator properties. It belongs to the group of potassium channel-opening vasodilators. Nicorandil possesses a dual mechanism of action: a nitrate-like effect, as well as potassium channel-opening properties. This study was designed and performed to evaluate and compare the clinical efficacy and safety of nicorandil versus conventional anti-anginal therapy in Iranian patients with established multivessel coronary artery disease.

Patients and methods- A double-blind, randomized placebo-controlled clinical trial recruited and randomly assigned 50 patients with established multivessel coronary artery disease into two groups (N=25): the first group receiving 10mg nicorandil twice daily plus conventional anti-anginal therapy and the second group taking conventional anti-anginal therapy plus placebo. The total duration of the study for each patient was 12 weeks. A symptom–limited exercise test was performed to evaluate ischemic variables at baseline and then at two consecutive 6-week intervals. Major coronary events as well as adverse drug reactions were recorded initially and in the middle as well as the termination of the study to assess the safety and tolerability of nicorandil.

Results- Both groups had comparable baseline values for exercise tests. During treatment, time to the onset of ST-segment depression increased in both groups; however, the difference compared to baseline was only statistically significant in the nicorandil group. Exercise time was increased during treatment and follow-up period. Patients’ improvement in the nicorandil group was obviously much more considerable compared with that in the placebo - conventional therapy group. No patient experienced exacerbation of angina during nicorandil treatment. As for safety and tolerability, the distribution and frequency of adverse events were not significantly different between the groups.

Conclusion- Our data suggest that nicorandil improves exercise capacity and can be considered an effective and safe anti-anginal agent as an add-on to conventional therapy in patients with multivessel coronary artery disease (Iranian Heart Journal 2004; 5(1,2):12-19).

Key words: nicorandil■ potassium channel openers■ angina pectoris■ clinical trial
Nicorandil, a recently introduced drug for the treatment of coronary heart disease (CHD), has well-described pharmacological properties.\textsuperscript{1,2} It was first developed in Japan in 1984, and it was approved in European countries and Australia during the 90's. Currently, this medication is undergoing phase III trials for FDA approval process.\textsuperscript{3}

Nicorandil belongs to the class of compounds known as potassium channel openers. Structurally, it is described as a hybrid compound consisting of a nicotinamide group and an organic nitrate moiety. Nicorandil induces vascular smooth muscle relaxation by a dual mechanism of action: first as an ATP-sensitive potassium channel opener, it increases the efflux of potassium ions from the cell. By opening potassium channels, there is an increased efflux of potassium ions from the cell and the resting membrane potential is shifted towards more negative values (hyperpolarisation), which leads to the inhibition of calcium influx or indirect calcium antagonism, causing a fall in intracellular calcium concentration, relaxation of vascular smooth muscle cells and vasodilation.\textsuperscript{3,4}

The dose-response relationship for vascular relaxation with nicorandil differs from that of other nitrovasodilators, suggesting that the opening of potassium channels makes a significant contribution to its vasodilatory properties. Secondly as a nitrate-like compound, nicorandil dilates venous capacitance vessels, increasing blood flow, and hence oxygen delivery to the ischemic myocardium via vasodilation of the coronary vasculature. Thus nicorandil reduces myocardial oxygen consumption by decreasing both preload (increased systemic vasodilation) and afterload.

Dose-response relationship for vascular relaxation with nicorandil differs from that of other nitrovasodilators, suggesting that the opening of potassium channels makes a significant contribution to its vasodilatory properties. Secondly as a nitrate-like compound, nicorandil dilates venous capacitance vessels, increasing blood flow, and hence oxygen delivery to the ischemic myocardium via vasodilation of the coronary vasculature. Thus nicorandil reduces myocardial oxygen consumption by decreasing both preload (increased systemic vasodilation) and afterload.

Nicorandil is hepatically metabolized and renally excreted, and is available both in parenteral and oral dosage forms. Previous potassium channel opening drugs such as minoxidil or diazoxide had basically arteriolar vasodilating properties, but nicorandil and new generation potassium channel openers, while preserving arteriolar dilatory effects, have pronounced coronary artery vasodilating properties. Coronary potassium channel openers such as nicorandil have anti-ischemic effects without causing systemic hemodynamic disturbances. Anti-ischemic effects of nicorandil in patients with CHD are apparent at dosages that do not evoke a pronounced decrease in systemic blood pressure or significant reflex tachycardia. Angiographic studies have shown that nicorandil dilates both stenotic and nonstenotic coronary arteries.\textsuperscript{5} It is not negatively inotropic, and it may therefore be used with relative safety in patients with non-severe left ventricular dysfunction.\textsuperscript{6}

Nicorandil is demonstrated to have enhanced exercise capacity in patients with ischemic heart disease. This benefit can be attributed to the reduction in loading of the right and left ventricles, as well as to an improvement of regional left ventricular wall motion abnormalities, a marker of myocardial function secondary...
It has also been suggested that nicorandil can induce pre-conditioning, a condition which offers powerful protection against ischemic necrosis and renders the medication to act as a cardioprotective agent. Hence, nicorandil may play an important role in bypass surgery and confer protection in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). The drug has also demonstrated potential cardioprotective effects when used as part of an intervention strategy directly after acute myocardial infarction. Recently, there has been numerous studies concerning nicorandil anti-apoptotic properties on cardiomyocytes as well as immunomodulating effects. Finally, nicorandil has been shown to prevent platelet aggregation.

These characteristics have justified its assessment as an anti-anginal compound in numerous clinical and experimental studies. Previous trials have demonstrated that oral nicorandil 10-20mg twice daily is effective and well tolerated in the treatment of stable angina pectoris. To date, however, trials assessing nicorandil compared with conventional anti-anginal therapy in Iranian patients with multivessel coronary artery disease have not been conducted. Thus the objective of this trial was to evaluate and compare the anti-anginal and anti-ischemic efficacy and tolerability of nicorandil with those of conventional therapy in patients with multivessel coronary artery disease.

Methods

Patients
Fifty men and women aged 42 – 85 years with definite electrocardiographic evidence of myocardial ischemia (ST-segment depression before exercise test) and established multivessel coronary artery disease (CAD) and in New York Heart Association (NYHA) functional classification III and IV taking conventional anti-anginal therapy (including nitrates, beta blockers and calcium channel blockers) were recruited for enrollment in the study. Eligible patients had a history of CAD for > 3 months, and their CAD was confirmed by angiography (3 vessel artery disease) with recommendation of medical management, and definite electrocardiographic evidence of myocardial ischemia. Exclusion criteria included: supine systolic blood pressure (SBP)<100 mmHg or DBP<70 mmHg; diabetes mellitus type II, necessitating administration of drugs with potassium channel blocking properties such as sulfonylureas, eg. glibenclamide and tolbutamide, and severe concomitant disease. The study process was explained clearly, and informed consent in writing was obtained from all of the patients prior to trial. The trial was performed in accordance with the Declaration of Helsinki (revised version, Hong Kong 1989).

Study design and organisation
The study had a randomized, placebo controlled, double-blind design and was conducted from Sept. 2002 to Oct. 2003. First a questionnaire was designed and prepared to record patients’ demographic information as well as their functional class, chest pain, dyspnea, etc. Following an initial screening visit, all the patients with established three vessel coronary artery disease who were deemed suitable for enrollment underwent a treadmill exercise test and afterwards were randomly assigned to two parallel groups for a 12-week treatment period (simple random sampling). In the first group (placebo controlled), the patients received conventional anti-anginal therapy without
Noricandil in Multi-Vessel CAD

F. Farsad, PhD, et al.

Conventional therapy included 10mg isosorbide dinitrate, 60mg dliltiazem, 5mg amlopidine, 40mg propranolol, 20mg enalapril and 25mg captopril, plus a 10mg inert placebo tablet. In the second group (drug group), the patients were given 10mg nicorandil twice daily plus conventional therapy as described above. The order was random and the treatment was completely blinded so that neither the patient nor the investigator knew which medication was taken. Before the definitive drug administration, all the patients underwent treadmill exercise tests. Patients returned to hospital at 6-week intervals for follow-up. The interim check exercise tests and clinical examinations were performed and repeated on days 0, 42 and 84 of the trial. The patients were asked to identify and report any adverse event at any time during the trial. Laboratory evaluation of paraclinical parameters (hemoglobin, hematocrit, sodium, potassium, creatinine, FBS, HDL and LDL, etc.) was conducted at the start, middle and end of the trial. The study protocol was approved by the local research and ethics committee.

Exercise testing
Exercise testing was performed under the same circumstances for all the patients. A symptom-limited exercise test was performed on a treadmill. The onset of anginal pain was indicated by the patient. Exercise was terminated when patients complained of moderate chest pain. Systolic and diastolic blood pressure was recorded during and immediately after exercise termination. A 12-lead electrocardiogram was conducted during exercise and recovery. Heart rate (HR) and ST-segment depression at rest as well as during exercise and recovery period were recorded. Exercise duration and the peak to ST depression were recorded as well.

Primary and secondary endpoints
The primary efficacy endpoint was established to be the total exercise stress test (EST) duration and peak to ST-segment depression (sec) during exercise testing. The secondary end point was the metabolic equivalents (METs).

Statistical analysis
A total of 25 patients per treatment group was required to detect a difference between the medications of 0.65 SD (standard deviation) of the difference, with a probability of 90% (power) at the a =5% level of significance. Paired t-test was used to analyze changes as compared to baseline. Data and results were expressed as means ± standard deviation values and proportions as percentages. The statistical level of significance was defined as a value of p<0.05 unless otherwise specified.

Results

Patient characteristics
A total of 50 patients were recruited for this study and were randomized (Table I).

Table I. Baseline demographic and clinical characteristics at the start of study (mean±SD).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>50:50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.25±7.4</td>
</tr>
<tr>
<td>NYHA functional classes</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>74%</td>
</tr>
<tr>
<td>IV</td>
<td>26%</td>
</tr>
<tr>
<td>Conventional therapy regimen</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>68%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>76%</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>26%</td>
</tr>
<tr>
<td>EST parameters</td>
<td></td>
</tr>
<tr>
<td>Time to onset of anginal pain(min)</td>
<td>4.9±0.4</td>
</tr>
<tr>
<td>Total exercise duration (min)</td>
<td>3.69±0.3</td>
</tr>
</tbody>
</table>

EST=Exercise Stress Test
One patient in the nicorandil group dropped out during treatment due to poor compliance. Baseline patient characteristics are given in Table I. Men constituted 52% (N=26) and 50% (N=25) of the case and control groups, respectively, and women comprised 48% (N=24) and 50% (N=25).

The two groups were similar in terms of the patients’ mean age. The patients were elderly and moderately to severely symptomatic (mean age 63.25±6.6). 76% of the patients were in NYHA functional classification III and 24% in class IV. Conventional anti-anginal therapies included beta-blockers (76%), nitrates (68%), calcium channel blockers (60%) and angiotensin converting enzyme inhibitors (ACEI’s) (56%), respectively, as the most commonly prescribed medications.

**Primary and secondary endpoints**

Time to onset of ST-segment depression increased in both groups during the study (Table II). However, the difference compared to baseline was only statistically significant in the nicorandil group.

**Table II. Primary and secondary endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Nicorandil Baseline</th>
<th>Nicorandil 6 weeks</th>
<th>Nicorandil 12 weeks</th>
<th>Placebo Baseline</th>
<th>Placebo 6 weeks</th>
<th>Placebo 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST depression</td>
<td>2.35</td>
<td>2.65</td>
<td>3.77</td>
<td>2.66</td>
<td>3.32</td>
<td>3.44</td>
</tr>
<tr>
<td>Peak to ST depression</td>
<td>4.56</td>
<td>5.92</td>
<td>7.48</td>
<td>3.69</td>
<td>3.30</td>
<td>2.76</td>
</tr>
<tr>
<td>Total EST duration</td>
<td>3.39</td>
<td>5.06</td>
<td>5.17</td>
<td>3.61</td>
<td>3.68</td>
<td>3.74</td>
</tr>
<tr>
<td>P value</td>
<td>0.05</td>
<td>0.01</td>
<td>0.05</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time to onset of angina pain and total exercise duration were significantly higher in all the patients at 26 and 12 weeks compared to baseline, while the magnitude of ST-segment depression at maximal identical workload was significantly decreased. Exercise time was increased from 3.39±2.6 minutes to 5.06±2 and 5.17±3 minutes in the 6-week and 12-week follow-up period, respectively (p< 0.01). Nevertheless, workload was increased from 4.56±2.7 METs to 5.92±2.3 and 7.48±2.1 METs in the 6-week and 12-week follow-up period.

**Safety and tolerability**

All the 50 patients who were randomized to receive study medications were included in safety analysis. A total of 3 adverse events were reported in the nicorandil group, while in the conventional group 8 adverse events were observed. The most common adverse events that were considered to be possibly related to treatments were mild ankle edema in the nicorandil group and headache in the conventional group (Table III). No death occurred during treatment in either nicorandil or conventional group.

No clinically relevant changes in laboratory parameters were apparent in either treatment group during the trial.

**Table III. Summary of adverse events reported during treatment with nicorandil or conventional therapy, which were considered to be probably related to medication.**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Nicorandil</th>
<th>Conventional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Flushing/huming face</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Trembling</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion**

**Clinical efficacy**
The present study confirms the antianginal property of nicorandil in multi-vessel coronary artery disease in terms of reducing the number of anginal episodes as well as increased exercise test capacity. Nicorandil has been extensively studied in Europe in more than 1500 patients with angina, both in placebo-controlled studies and in comparative studies with other antianginal agents. The majority of studies show that nicorandil is superior to placebo in reducing angina episodes and increasing exercise duration. In four double-blind placebo-controlled trials, patients receiving oral nicorandil experienced significant improvements in exercise time to the onset of angina and total attainable workload. Comparative studies also suggest that nicorandil has equivalent efficacy to nitrates, beta-adrenergic antagonists and certain calcium channel blockers for reducing both ischemic and anginal symptoms.

The largest major outcome study to date on the cardiovascular properties of nicorandil has been the Impact of Nicorandil on Angina trial (IONA), involving 5126 patients with stable angina. The patients were randomized to placebo or nicorandil 10mg bd, titrated upward to 20mg bd and were followed for 12 to 36 months. Based on the IONA study, nicorandil was shown to lower the risk of the primary end point of cardiovascular death, myocardial infarction or unplanned hospitalization for angina by 17%. The incidence of all adverse cardiovascular events was significantly reduced.

**Safety profile**

In this study, no significant adverse effect leading to the drug’s discontinuation was recorded. Nicorandil was superior to conventional therapy in terms of side effects profile. One cutaneous flare up was reported in the nicorandil group, which could be due to the administration of captopril. Nicorandil was well tolerated in the elderly, and no special dose adjustment was required. In addition, the drug had no interaction with anticoagulants or hepatic metabolism inhibitors such as cimetidine. As it was indicated in exclusion criteria, taking nicorandil with medications with potassium channel blocking properties must be avoided.

There appears to be a relatively large gap between the results of our center with those of other trials studying the safety profile of nicorandil. Unexpectedly in this study, the most prevalent adverse drug reaction was ankle edema, contrary to other trials, which had indicated headache as the most common adverse reaction. This could be due to the lower dosage of nicorandil used in our trial (10 mg twice daily) compared with that in other studies. Similarly, nicorandil had no apparent effect on BP in this study, either at rest or during ETT. It merits emphasis once more that the patients were maintained on the low-dose regimen and that our findings were not unexpected.

Long-term safety of nicorandil has been extensively assessed. In 1700 subjects treated with nicorandil, headache was the adverse event most often encountered. Headache with nicorandil usually occurs early during treatment and disappears with chronic use. Some of the discrepancy between our results and the above-mentioned studies can be attributed to our short follow-up period as well as a smaller number of patients.

Despite the fact that the hemodynamic effects of both nitroglycerin and nicorandil are mediated by the same system (nitrous oxide synthesis), the present study suggests that anti-anginal and hemodynamic tolerance to nicorandil does not develop to a significant degree.

Nicorandil may also have a role in managing individuals with underlying...
obstructive airway disease, dyslipidemia or diabetes, where a beta-blocker is inappropriate. Similarly, it may prove useful in patients who are difficult to manage with drugs which increase heart rate, or where nitrate tolerance is a problem.

**Conclusion**

In conclusion, nicorandil apparently can be used effectively and safely as an add-on to nitrates, beta-blockers and calcium channel blockers in patients with multi-vessel coronary artery disease. It may be useful in patients who are difficult to manage and are refractory to conventional anti-anginal agents. It may be beneficial in patients who cannot tolerate either of the above agents, particularly those who feel lethargic on beta blockers or have profound ankle edema on calcium antagonists. On the other hand, it may be less useful for those who are headache prone. Final judgement on widespread employment of nicorandil in the treatment of coronary artery disease requires further considerations such as cost and reimbursement issues.

**Acknowledgements**

The authors wish to thank Ms. Golshan and Ms. Samini for the secretarial preparation of the manuscripts. This work was presented at the 3rd Congress of Iranian Society of Cardiac Surgeons, Sept. 2003, Tehran, Iran.

**References**


8. Wei XM, Heywood GJ: Nicorandil inhibits the release of TNF alpha from a lymphocyte cell line and peripheral blood lymphocytes. Int Immunopharmacol. 2003 Nov; 3 (12); 1581-8.


