

Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction

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Objective: To compare the effects of nicorandil (a hybrid ATP sensitive potassium channel (K^+_{ATP} channel) opener/nitric oxide donor) with those of isosorbide dinitrate (ISDN) on myocardial microcirculation and cardiac function in patients with acute myocardial infarction (AMI) who had undergone reperfusion treatment by direct balloon angioplasty.

Design: Double blind randomised study.

Patients: 60 patients with AMI in Killip class I.

Interventions: Patients were assigned into two treatment groups: a nicorandil group (n = 30) and an ISDN group (n = 30). Each drug was infused intravenously at 6 mg/h for 72 hours starting at admission and was administered directly to the treated coronary artery immediately after angioplasty.

Results: Compared with ISDN, nicorandil more frequently caused recovery of ST segment elevation just after reperfusion (15 of 27 (55.5%) in the nicorandil group v 5 of 26 (19.2%) in the ISDN group, p = 0.006). The nicorandil group had higher values of averaged peak velocity 40 minutes after reperfusion (mean (SD) 24.8 (13.3) cm/s v 16.0 (11.1) cm/s, p = 0.045) and higher values of regional wall motion of the infarcted area three weeks after onset of AMI (-1.78 (1.11) v -2.50 (1.04) SD/chord, p = 0.046).

Conclusions: A combination of nicorandil drip infusion starting before reperfusion and intracoronary injection immediately after reperfusion is more effective than a similarly performed infusion of ISDN in preserving myocardial microcirculation in the reperfused AMI area. The nicorandil regimen resulted in better left ventricular regional wall motion.

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Coronary reperfusion is now widely used to restore blood flow to the jeopardised myocardium in patients with acute myocardial infarction (AMI). However, several studies have shown that about 20% to 35% of angiographically successful recanalizations of an infarct related artery fail to salvage ischaemic myocardium.¹⁻³ This unfavourable outcome is related to a discrepancy between an open epicardial coronary artery and the absence of blood flow (no reflow) in the damaged distal microvessels.

Nicorandil, a hybrid molecule comprising an ATP sensitive potassium channel (K^+_{ATP} channel) opener and a nitric oxide donor, has been approved as a treatment for angina pectoris in Japan and Europe. Recently, a large clinical trial, the IONA (impact of nicorandil on angina) study,⁴ showed that nicorandil reduces the frequency of cardiovascular events in patients with stable effort angina compared with placebo. Nicorandil promotes the recovery of post-ischaemic contractile dysfunction and reduces infarct size in animals.⁵⁻⁸ Numerous mechanisms for the salutary actions of nicorandil have been postulated, including reduction of preload and afterload, anti-free radical and neutrophil modulating properties,⁹⁻¹¹ vasodilatation of small coronary arteries, and mimicking of ischaemic preconditioning.¹² Nitric oxide donors such as isosorbide dinitrate (ISDN) also exert a cardiac protective action during ischaemia-reperfusion.^{13, 14} In previous studies, nicorandil improved functional and clinical outcomes compared with coronary reperfusion alone in patients with AMI.¹⁵⁻¹⁷ However, no double blinded trials have compared the effects of nicorandil and of ISDN in patients with AMI.

The aim of this study was to assess the effects of nicorandil on microcirculation, functional improvement, and in-hospital

complications and to compare these effects with those of ISDN, a more potent nitric oxide donor.¹¹ To assess myocardial perfusion, coronary flow velocity was measured with a Doppler guidewire.

METHODS

Patient selection

From October 1998 to March 2000, a total of 209 consecutive patients with AMI were admitted to our coronary care unit. Patients eligible for this study were men and women < 80 years of age with a history of chest discomfort over 30 minutes in duration associated with ST segment elevation of more than 0.2 mV in at least two contiguous leads. Maximum serum concentrations of creatine kinase more than twice the upper limit of normal and admission within 12 hours after symptom onset were required for inclusion. Patients were excluded if they were in Killip grade II or higher or had a history of AMI or prior coronary bypass surgery. Of these, 60 patients (42 men, 18 women; mean (SD) age 63 (9) years) who fulfilled the inclusion criteria were enrolled in the present study. These 60 patients were randomly assigned to two treatment groups in a double blind fashion: the nicorandil group (n = 30) and the ISDN group (n = 30). The study protocol was approved by the ethical committee of Jichi Medical School and written informed consent was obtained from each patient.

Abbreviations: AMI, acute myocardial infarction; IONA, impact of nicorandil on angina; ISDN, isosorbide dinitrate; K^+_{ATP} channel; ATP sensitive potassium channel; TIMI, thrombolysis in myocardial infarction

Table 1 Clinical characteristics of the study patients

	Nicorandil (n=30)	ISDN (n=30)	p Value
Mean age (years)	60 (9)	63 (10)	0.38
Male sex	23/30 (76.7%)	25/30 (83.3%)	0.52
Diabetes mellitus	5/30 (16.7%)	6/30 (20.0%)	0.74
Preinfarction angina (<48 h)	14/30 (33.3%)	12/30 (40.0%)	0.80
Mean time from onset to reperfusion (h)	5.2 (2.5)	5.7 (3.3)	0.47
Anterior MI	10/30 (33.3%)	12/30 (40.0%)	0.59
Non-Q MI	2/30 (6.6%)	1/30 (3.3%)	0.59
TIMI grade (0, 1) before angioplasty	(26, 4)	(25, 5)	0.72
TIMI grade (2, 3) after angioplasty	(1, 29)	(3, 27)	0.30
Collateral (grade > 2)	3/30 (10.0%)	2/30 (6.7%)	0.64
ACE inhibitor	14/30 (46.7%)	15/30 (50.0%)	0.79
β Blocker	5/30 (16.6%)	7/30 (23.3%)	0.52
Mean BP (mm Hg)	92 (9)	89 (7)	0.33
Mean HR (beats/min)	79 (11)	78 (12)	0.96
Use of stent	1/30 (70.0%)	19/30 (63.3%)	0.58
Maximum CK concentrations (iu/l)	2953 (1950)	3595 (2274)	0.25

Values are mean (SD) or number (%).

ACE, angiotensin converting enzyme; BP, blood pressure; CK, creatine kinase; HR, heart rate; ISDN, isosorbide dinitrate; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Study design

This study was designed as a prospective, double blind, randomised trial in a single centre. One of the investigators supervised the double blind study as a safety and data monitor.

Protocol

Immediately after diagnosis of AMI, the study drug (nicorandil or ISDN) was infused intravenously at 6 mg/h for 72 hours. All patients underwent emergent cardiac catheterisation through a femoral artery after injection of 3000 U of heparin. Each patient received 162 mg of aspirin and an additional 7000 U of heparin before angioplasty. Stents were implanted if unsatisfactory angioplasty results were obtained. Stented patients received ticlopidine (200 mg twice a day) and aspirin (81 mg), whereas non-stented patients were given aspirin only. Successful reperfusion was defined as thrombolysis in myocardial infarction (TIMI) grade 2 or higher, as determined by angiography. Immediately after confirmation of successful coronary reflow, the study drug (2 mg) was administered into the treated coronary artery. We used a combination of intravenous drip infusion starting at the time of diagnosis of AMI

and intracoronary artery infusion immediately after angioplasty to elicit maximal effects of the study drugs as adjunctive treatments. Because abrupt activation of K^+_{ATP} channels has been shown to be proarrhythmic,¹⁸ we slowly injected both drugs into the treated coronary artery over a period of 60 seconds. Heparin infusion was continued for 72 hours and systolic blood pressure was kept below 150 mm Hg by intravenous drip infusion of nicardipine after angioplasty. Systemic blood pressure and the pulse in the left arm were measured by specially trained nurses at 7 am, noon, 5 pm, and 9 pm every day during the first seven days. The results of all 28 measurements were averaged. Serum concentrations of creatine kinase were measured every four hours from admission until they peaked and began to fall. The decision of whether to administer angiotensin converting enzyme inhibitors and β blockers was left to the attending physician. Cardiac catheterisation was repeated three weeks after onset of AMI.

Outcome assessment

The total ST segment elevation excluding aVR (defined as \sum ST) was measured when TIMI 0 or 1 flow was confirmed before reperfusion. The \sum ST was also examined when TIMI 2 or 3 flow was confirmed for the first time after reperfusion by angioplasty. The isoelectric line was selected at the level of the PQ junction and ST segment elevation was measured at the J point. Posterior and lateral AMIs ($n = 7$) were excluded from the electrocardiographic analysis. The change in \sum ST at reperfusion was classified into one of the following two groups according to degree: decrease of $\geq 20\%$ (ST recovered); and decrease of $< 20\%$ or increase (ST not recovered) as described previously.¹⁹

The status of the collateral circulation was defined as reported by Rentrop and colleagues.²⁰ Left ventriculography was performed about 30 minutes (21–40 minutes) after the reperfusion and three weeks after the onset of AMI. One observer without knowledge of the patients' data carefully traced all left ventricular end diastolic and end systolic endocardial contours. Left ventricular end diastolic volume index and end systolic volume index were determined. Global left ventricular ejection fraction was determined by the area-length method. Regional left ventricular wall motion was measured by the centre line method and expressed as SD/chord, as described elsewhere.^{21–22} Posterior and lateral AMIs were excluded from regional wall motion analysis.

Coronary blood flow velocity was measured about 40 minutes (31–60 minutes) after the reperfusion with a

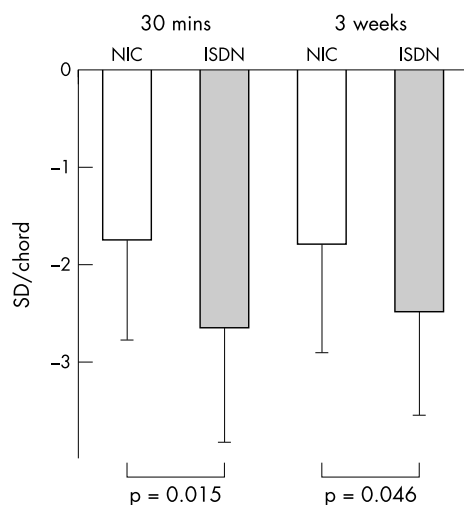


Figure 1 Regional wall motion was analysed by the centre line method and expressed as SD/chord. SD/chord 30 minutes after reperfusion and three weeks after onset was significantly lower in the nicorandil (NIC) group than in the isosorbide dinitrate (ISDN) group.

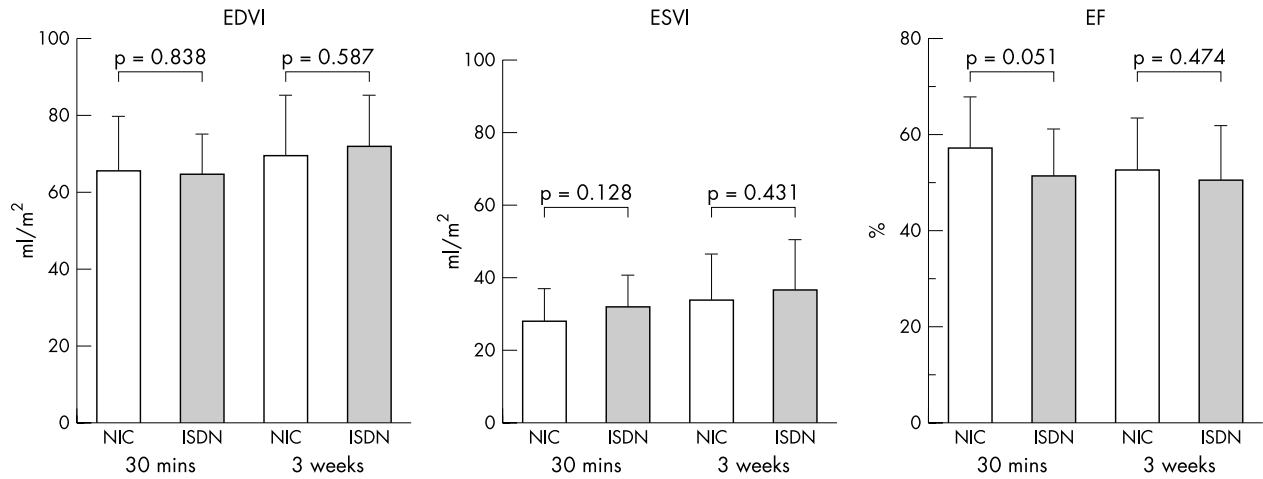


Figure 2 Left ventricular volume (EDVI and ESVI) and global ejection fraction (EF) in left ventriculography are shown. There were no differences in left ventricular volume between the two treatment groups.

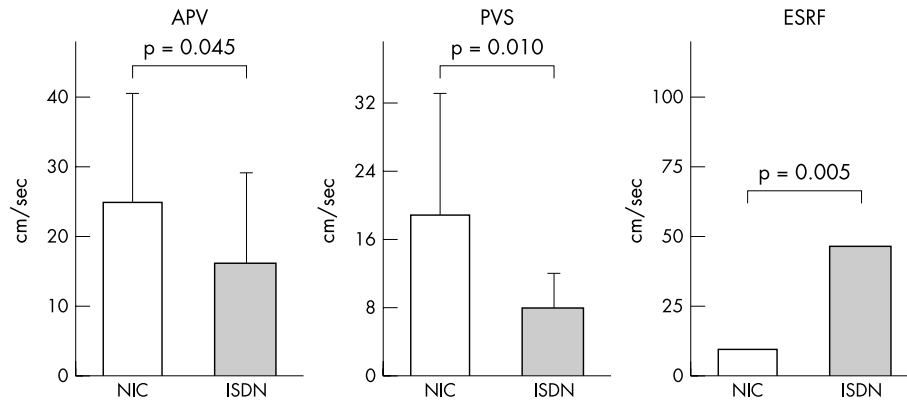


Figure 3 Data from coronary flow measurements are shown. Averaged peak velocity (APV) and peak systolic antegrade flow velocity (PVS) were higher in the NIC group than in the ISDN group. Frequency of early systolic retrograde flow (ESRF) was lower in the NIC group.

Doppler guidewire connected to a real time spectrum analyser, as described elsewhere.²³ Time averaged peak velocity was computed on line and continuously recorded on videotape. The peak systolic antegrade flow velocity and frequency of early systolic retrograde flow were also analysed.

Statistical analysis

Data are presented as mean (SD). Groups were compared with Student's *t* test or analysis of variance with Fisher's post hoc test for continuous variables and χ^2 test for categorical values, as appropriate. A probability value of $p < 0.05$ was considered to indicate significance.

RESULTS

Baseline characteristics

There were no significant differences between the nicorandil and ISDN group with regard to age, sex, diabetes, preinfarction angina, infarction site, TIMI grade before and after angioplasty, collateral grade, time from onset to reperfusion, blood pressure, heart rate, use of stents, administration of angiotensin converting enzyme inhibitors and β blockers, or maximum serum concentrations of creatine kinase (table 1).

Electrocardiogram

Nicorandil more frequently caused recovery of ST segment elevation just after reperfusion (15 of 27 (55.5%)) than did ISDN (5 of 26 (19.2%), $p = 0.006$).

Left ventriculography

Regional wall motion of the infarct area 30 minutes after reperfusion was significantly greater in the nicorandil group than in the ISDN group (mean (SD) -1.75 (1.03) *v* -2.66 (1.16) SD/chord, $p = 0.015$). This effect continued for the three weeks after the onset of AMI (-1.78 (1.11) *v* -2.50 (1.04) SD/chord, $p = 0.046$) (fig 1). There were no differences in left ventricular volume between the two treatment groups (fig 2).

Coronary flow measurements

Of the coronary flow velocity variables measured 40 minutes after reperfusion, averaged peak velocity (24.8 (13.3) *v* 16.0 (11.1) cm/s, $p = 0.045$) and peak systolic antegrade flow velocity (18.8 (12.9) *v* 7.9 (4.2) cm/s, $p = 0.010$) were significantly higher in the nicorandil group than in the ISDN group (fig 3). The frequency of early systolic retrograde flow was significantly lower in the nicorandil group (4 of 30 (13.3%) *v* 14 of 30 (46.7%), $p = 0.005$) (fig 3).

Table 2 Major complications

	Nicorandil (n=30)	ISDN (n=30)	p Value
Sustained VT (rate > 100 beats/min)	1/30 (3.3%)	2/30 (6.7%)	0.55
Pericardial effusion	3/30 (10%)	5/30 (16.6%)	0.25
Ventricular rupture	0/30 (0%)	1/30 (3.3%)	0.32

VT, ventricular tachycardia.

Complications

After the intracoronary injection of nicorandil, slow ventricular tachycardia (rate < 100 beats/min, also known as accelerated idioventricular beats) appeared in three patients but did not cause deterioration of the circulatory condition. There was no significant difference in the number of patients with sustained ventricular tachycardia (rate \geq 100 beats/min), which required direct current cardioversion. Ventricular fibrillation was not seen in any patient during the study period. There was no significant difference in the incidence of pericardial effusion between the treatment groups. One patient in the ISDN group had a ventricular free wall rupture. He underwent an urgent surgical repair and was discharged (table 2). There were no deaths during the study period. Patients did not experience congestive heart failure or post-infarction angina during hospitalisation.

DISCUSSION

This double blind trial showed nicorandil to be more effective than ISDN in preserving left ventricular regional function at three weeks after AMI.

Nicorandil more frequently caused recovery of ST segment elevation just after reperfusion. We previously reported ST segment elevation after reperfusion as an index for predicting improvement of left ventricular systolic function in patients with reperfused anterior AMI.¹⁹ There was no difference between the treatment groups in regard to time from onset to reperfusion, existence of preinfarction angina, or grade of collateral vessels. Regional wall motion of the infarcted area at 30 minutes after reperfusion was higher in the nicorandil group than in the ISDN group, and this effect continued for the three weeks after the onset of AMI. This suggests that nicorandil mimics ischaemic preconditioning or suppresses reperfusion injury involving reversible ischaemia-reperfusion injury ("stunned myocardium").⁵

Restoration of myocardial perfusion immediately after coronary revascularisation is an important mechanism for salvaging the post-ischaemic myocardium.² According to a double blind study of 300 patients with AMI who underwent coronary angiography, abciximab, a glycoprotein IIb/IIIa antagonist, plus stenting improved the primary end point (a composite of death, reinfarction, or urgent revascularisation of the target vessel), TIMI flow classification before and after stenting, and left ventricular function six months after onset compared with placebo plus stenting.²⁴ Abciximab has not been approved in Japan yet and the cost effectiveness of this drug requires further study before it can be used routinely.²⁵ In previous studies, salutary actions of nicorandil on the coronary microvasculature were assessed by myocardial contrast echocardiography.¹⁵⁻¹⁶ In the present study, coronary flow velocity was measured with a Doppler guide-wire to assess myocardial perfusion. Iwakura and colleagues²³ found a strong correlation between no reflow (shown by myocardial contrast echocardiography) and early systolic retrograde flow (measured by Doppler guidewire). The nicorandil group had a higher coronary flow velocity after reperfusion and a lower frequency of early systolic retrograde flow than the ISDN group. Dilatation of smaller arterioles is an important factor in the extent of myocardial stunning,²⁶⁻²⁷ infarct size, and functional recovery²⁸⁻²⁹ after ischaemia-reperfusion. K^+ ATP channel activators dilate resistant vessels (especially arterioles with diameters < 100 μ m)³⁰⁻³¹ and increase collateral blood flow.³²⁻³³ In contrast, pure nitric oxide donors such as ISDN do not dilate small arteries and arterioles with diameters < 100 μ m. Leucocytes are key players in the aggravation of post-reperfusion microcirculation through mechanisms such as spasm of microvessels, leucocyte plugging in microvessels, and production of oxyradical mediators.³⁴⁻³⁵ In a recent study we conducted

with in vivo and in vitro methods,¹⁴ nicorandil and a specific mitochondrial K^+ ATP channel opener (diazoxide) suppressed the following processes of leucocyte activation: leucocyte pseudopod formation in the presence of *N*-formyl-methionyl-leucyl-phenylalanine under shear stress; adhesion of leucocytes to postcapillary venular endothelial cells; and extravascular migration of leucocytes in rat mesenteric microvessels subjected to ischaemia-reperfusion. An increase in shear rate caused by increased microvessel flow induced by a K^+ ATP channel activator may also reduce neutrophil recruitment³⁶ because leucocyte attachment to and migration through inflamed vessels is somewhat dependent on shear rate. In addition, Gross *et al*⁹ and Pieper *et al*¹⁰ found that the beneficial effects of nicorandil in recovery from ischaemia-reperfusion injury may be due partly to inhibition of free radical production by leucocytes.

In a recent large clinical trial (n = 5126),⁴ nicorandil significantly reduced the number of cardiovascular events in patients with stable effort angina compared with placebo (relative risk reduction 15%, p = 0.025) during a follow up period of up to three years. This supports the benefit of pharmacological preconditioning in the management of stable angina. In addition, recent experiments³⁷⁻³⁸ with knockout mice have clearly documented that K^+ ATP channel subunits Kir 6.2 and sulfonylurea receptor 2 have important roles in preventing fatal vasospastic angina.

Conclusion

Nicorandil administered in a combination of drip infusion starting during the ischaemic period and intracoronary injection immediately after reperfusion was more effective than a similarly performed infusion of ISDN in preserving the myocardial microcirculation in relatively low risk patients with AMI. The result was improved left ventricular wall motion in the infarction zone. The present results suggest the need for a large clinical trial to determine whether nicorandil should be recommended for patients with AMI.

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Prognosis of angina with and without a diagnosis: 11 year follow up in the Whitehall II prospective cohort study

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Objective: To investigate the prognosis of angina among people with and without diagnosis by a doctor and an abnormal cardiovascular test result.

Design: Prospective cohort study with a median follow up of 11 years.

Setting: 20 civil service departments originally located in London.

Participants: 10 308 civil servants aged 35–55 years at baseline.

Main outcome measures: Recurrent reports of angina; quality of life (SF-36 physical functioning); non-fatal myocardial infarction; death from any cause (n = 344).

Results: 1158 (11.4%) participants developed angina, and 813 (70%) had no evidence of diagnosis by a doctor at the time of the initial report. Participants without a diagnosis had an increased risk of impaired physical functioning (age and sex adjusted odds ratio of 2.36 (95% confidence interval 1.91 to 2.90)) compared with those who had neither angina nor myocardial infarction throughout follow up. Among reported cases of angina without a diagnosis, the 15.5% with an abnormality on a study electrocardiogram had an increased risk of death (hazard ratio 2.37 (1.16 to 4.87)). These effects were similar in magnitude to those in participants with a diagnosis of angina.

Conclusion: Undiagnosed angina was common and had an adverse impact on prognosis comparable to that of diagnosed angina, particularly among people with electrocardiographic abnormalities. Efforts to improve prognosis among people with angina should take account of this submerged clinical iceberg.

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