

BMJ Open Efficacy of intravenous nicorandil for fractional flow reserve assessment: study protocol for a crossover randomised trial

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ABSTRACT

Introduction: Nicorandil has vasodilatory effects on both the epicardial coronary arteries and the coronary microvasculature, thereby increasing coronary blood flow. Intravenous administration of nicorandil can be applicable for fractional flow reserve (FFR) measurement as a hyperaemic agent and a possible alternative to adenosine. However, the effectiveness of intravenous nicorandil infusion for FFR measurement is largely unclear.

Methods and analysis: This crossover randomised study is being performed to investigate the efficacy of intravenous administration of nicorandil for FFR measurement. Patients with an intermediate coronary artery stenosis who satisfy the eligibility criteria undergo FFR measurement with a consecutive randomised order of patient-blind infusions of continuous intravenous administration of adenosine and a single bolus intravenous administration of nicorandil. The primary end point of the study is the agreement between the FFR values obtained by the intravenous nicorandil and those obtained by the intravenous adenosine. Recruitment of this trial started in November 2015 and will end in March 2017, or until a total of 50 participants have been recruited.

Ethics and dissemination: The protocol was approved by the Institutional Review Board at Chiba University Hospital. Study findings will be published in peer-reviewed journals.

Trial registration number: UMIN000019309; Pre-results.

INTRODUCTION

Fractional flow reserve (FFR) is the gold standard in catheterisation laboratories to assess the physiological severity of coronary artery stenosis. FFR-guided therapy has been shown to improve patient outcomes by determining the appropriate selection of patients for percutaneous coronary intervention (PCI).^{1–3} FFR is defined as the ratio of maximal myocardial blood flow down a

Strengths and limitations of this study

- This crossover randomised trial is the first to investigate the efficacy of intravenous nicorandil for fractional flow reserve measurement in comparison to intravenous adenosine.
- Potential limitation of the trial is that the hyperaemic efficacy of a higher dosage of nicorandil is not evaluated in this study.
- If this study shows the feasibility of using intravenous nicorandil as a hyperaemic method, it can serve as a platform for further evaluation in a larger population.

coronary artery in the presence of an epicardial stenosis compared with the maximal flow down the same vessel in the theoretical absence of any stenosis.⁴ Owing to the linearity between hyperaemic pressure and blood flow, FFR can be calculated by measuring the mean distal coronary pressure (Pd) and dividing it by the mean proximal coronary pressure during maximal hyperaemia under the assumption that venous pressure is negligibly low.^{5 6} For an accurate calculation of FFR, achieving maximal coronary hyperaemia is an essential prerequisite.⁷ If maximal hyperaemia is not present, the distal coronary pressure will not decrease to its full extent, which will lead to the underestimation of stenosis severity. With this aim, intravenous administration of adenosine is currently considered as the gold standard method in clinical practice. However, adenosine has potential limitations, such as non-zero contraindications and side effects.⁸ In addition intravenous administration of adenosine is costly and requires added time, even though it can be minimised in well-organised catheterisation laboratories, for set-up and achieving hyperaemia.⁹ Therefore, in some situations, an



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alternative hyperaemic agent would be required to optimise FFR measurement.

Nicorandil is a 2-nicotinamidoethyl nitrate ester, a hybrid compound derived from an ATP-sensitive potassium channel (K-ATP channel) opener and a nitric oxide donor, and has been found to exert vasodilatory effects on both the epicardial coronary artery and the coronary microvasculature, thereby increasing coronary blood flow.^{10–12} Intravenous administration of nicorandil has been used for the treatment of angina pectoris and acute heart failure.^{13 14} In light of these, it could also be applicable for FFR measurement as a hyperaemic agent and a possible alternative to adenosine. However, the efficacy of intravenous administration of nicorandil for FFR measurement has been largely untested.

Thus, the objective of the proposed study is to investigate the efficacy and safety of intravenous administration of nicorandil as a novel hyperaemic method for FFR measurement in comparison to intravenous administration of adenosine as a reference standard.

METHODS

Trial design

This is a single-centre, prospective, single-blind, cross-over, randomised trial comparing the hyperaemic efficacy of intravenous administration of nicorandil with that of adenosine in patients with coronary artery disease undergoing FFR measurement.

Eligibility criteria

Eligible patients are those who meet all of the inclusion criteria mentioned below and none of the listed exclusion criteria. Inclusion criteria are patients with angiographically intermediate coronary artery lesions defined as 40–80% stenosis on the basis of visual estimation, aged between 20 and 89 years; and willing and able to give written informed consent.

Exclusion criteria include any of the following: acute coronary syndrome within the previous week; vessels with prior myocardial infarction; allergy to adenosine or nicorandil; asthma or chronic obstructive pulmonary disease on medical treatment; second or third degree atrioventricular block; severe valvular heart disease; acute decompensated heart failure; reduced left ventricular function (ejection fraction $\leq 30\%$); severe liver dysfunction; severe renal insufficiency; angle-closure glaucoma; patients who are taking phosphodiesterase type 5 (PDE5) inhibitors; and pregnancy.

Recruitment

Recruitment of this trial started in November 2015 and will end in March 2017, or until a total of 50 participants have been recruited. This study is being conducted at Chiba University Hospital.

Sample size calculation

The target sample size for this randomised trial is 50. This number is based on feasibility and following validity. Primary analysis of this study is to evaluate the agreement of the FFR values between the two drugs using the Bland-Altman plot.¹⁵ The estimated SD of the mean FFR value is 0.1 based on previous studies.^{16–19} The sample size, 50, will give a 95% CI of 95% limits of agreement (LOA) about ± 0.048 ,²⁰ which is sufficiently narrow and appropriate to assess the similarities with adequate accuracy.

Allocation

A registration form for each eligible patient will be sent by the investigators to the Data Management Centre at Chiba Clinical Research Centre (CCRC). Registration and group allocation will be implemented at the Data Management Centre, with one group receiving nicorandil followed by adenosine, and the other group receiving adenosine followed by nicorandil. Eligible patients with appropriately signed informed consent will be randomised to either the nicorandil-first group or the adenosine-first group at a ratio of 1:1, by employing a minimisation method with biased coin method balancing for the target vessel (left anterior descending (LAD) or non-LAD), and age (≥ 65 or < 65 years). Investigators will perform FFR measurement using adenosine and nicorandil in an administration order according to the allocation at the data management centre.

Interventions

The schedule for the study and data collection is summarised in [table 1](#).

Catheterisation procedure and FFR measurement

Coronary angiography with 5-F or 6-F guiding catheters without side holes will be performed using either the radial, brachial or femoral artery approach in standard multiple views by experienced operators. All patients will receive a bolus of heparin (at least 2000 IU) before the procedure. Then, a 0.014 inch pressure-monitoring guidewire (St. Jude Medical) will be externally calibrated and advanced through the guiding catheter into the tip of the guiding catheter, and it will be verified that the measured pressures in the pressure wire and the guiding catheter are equal. The wire will be then placed distal to the stenosis to measure distal coronary pressure, while careful attention will be paid to avoid arterial pressure dampening by disengaging the guiding catheter from the coronary ostium. Pd and mean aortic pressure (Pa) will be then measured at baseline and during hyperaemia induced by the drugs as mentioned below. FFR will be calculated as a ratio of Pd to Pa during hyperaemia and reported as an average of 5 cardiac cycles. Additionally, heart rate, aortic pressure, distal coronary pressure, ECG changes, and symptoms (namely a chest pain, dyspnoea, flushing, or headache) will be continuously monitored and recorded at baseline and during hyperaemia. The

Table 1 Schedule of study data collection

	Screening period registration	FFR measurement period		
		Baseline	Adenosine	Nicorandil
Informed consent	○			
Baseline characteristics	○			
Adverse event assessment		●	●	●
Vital signs*	○	●	●	●
Signs and symptoms	○	●	●	●
Haematological tests†	○			
Blood biochemical test‡	○			
ECG	○	●	●	●
Echocardiography	○			
Chest X-ray	○			
Coronary angiography	○			
Concomitant drug	○			
Pd, Pa recording		●	●	●
Time to hyperaemia			●	●
Fluctuation§			●	
Plateau time				●

○: To be performed before enrolment.

●: To be performed after enrolment; preformed consent data may also be used.

*Blood pressure, and pulse (respiratory rate and peripheral oxygen saturation (SpO₂) as necessary).

†White cell count, red blood cell, haemoglobin, haematocrit, platelet count.

‡Aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, C reactive protein, potassium, creatinine, chloride, sodium, creatine kinase, blood urea nitrogen, estimated glomerular filtration rate, brain natriuretic peptide, troponin I.

§Fluctuation is defined as changes in FFR value more than 0.05 during hyperaemic status by continuous adenosine infusion.

FFR, fractional flow reserve; Pa, mean aortic pressure; Pd, mean distal coronary pressure.

decision for treatment of any lesion will be left to operator's discretion by reference to the FFR values during intravenous infusion of adenosine.

Pharmacological protocol

To induce hyperaemia, intravenous administration of adenosine (Adenoscan, Fujisawa Healthcare) and intravenous administration of nicorandil (Sigmart, Chugai Pharmaceutical, Tokyo, Japan) will be in a consecutive randomised patient-blind order. Both drugs will be administered through a large central intravenous access in the femoral vein, internal jugular vein or subclavian vein; or through a 3-F or 4-F sheath or catheter inserted via the large cubital vein. The intravenous infusion of adenosine will be a standard 140 µg/kg/min continuous infusion for at least 2 min. The nicorandil will be administered by intravenous bolus injection over a 10 s period followed by 0.9% saline flush over a 10 s period. There will be at least a 5 min wash-out period between the intravenous nicorandil and intravenous adenosine administration to ensure that changes in hemodynamic parameters (coronary pressure, heart rate, aortic pressure) return to baseline level. A single FFR value per each drug will be measured in every patient. The lowest FFR values obtained during steady-state infusion of adenosine and within 5 min after a single infusion of nicorandil will be adopted as the lesion's representative FFR of each hyperaemic method. In all patients, intracoronary (IC) isosorbide dinitrate (at least 0.5 mg) will be administered before coronary angiography and

before each hyperaemic method. The venous line and the guide catheter are properly flushed between the infusions of each hyperaemic agent.

Quantitative coronary angiography

Quantitative coronary angiography will be performed by an independent analyser blinded to the results of FFR. Using the guide catheter for calibration and an edge detection system (QAngioXA V.7.1, Medis, Leiden, The Netherlands), the reference vessel diameter and minimum lumen diameter are measured, and the per cent diameter of stenosis will be calculated.

Blinding

The drug administration will be performed in a randomised order and will be patient-blinded, but not blinded to the operator.

End point

The primary end point of the study is the agreement of the FFR values obtained by the intravenous nicorandil and those obtained by the intravenous adenosine. The secondary end points include the number of functionally significant stenoses (FFR <0.75 or ≤0.80),^{1 2} the time to hyperaemia (time needed to reach <90% of the minimal value of Pd/Pa after the injection of the vasodilator), the plateau time (the time during which Pd/Pa ratio remained at <90% of its minimal value) after the intravenous administration of nicorandil, the frequency of fluctuation (change in FFR value more than 0.05

during hyperaemic status), hemodynamic parameters, ECG changes and symptoms during hyperaemia, and the frequency of adverse events.

Data management and monitoring

The investigators will maintain individual records for each patient as source data, which include a log of informed consent forms, medical history, laboratory data and other records, as appropriate. All entries in the case report forms (CRFs) will be backed up by the relevant source data. All data will be collected by the Data Management Centre at CCRC. The clinical data entry, coding, data management and reporting will be performed using the data management system, University Hospital Clinical Trial Alliance Clinical Research Supporting System (UHCT ACRess). Monitors will ensure that the investigational team is complying with the study protocol and Good Clinical Practice (GCP) standards. Investigators must record all adverse events in the patients' CRFs. The National Cancer Institute's CTCAE (V.4.0) will be used to grade each adverse event. All adverse events will be followed up during their course and until their resolution, or for 4 weeks after the end of the trial. An interim analysis will not be performed.

Statistical methods

The analyses of the primary and secondary outcomes will be performed in the full analysis set. For the baseline characteristics, summary statistics will be constructed using frequencies and proportions for categorical data, medians and IQRs for ordinal variable, and means and SDs for continuous variables.

For the primary analysis, the agreement of FFR values between intravenous nicorandil and the intravenous adenosine will be assessed using the Bland-Altman plot. The agreement will be considered to be high when the difference of FFR values between the two drugs is not large and systemic. The adjusted mean difference between FFR values, its 95% CIs, and p value will be calculated using an analysis of variance (ANOVA) model. The model will include groups (the nicorandil-first group or the adenosine-first group), individuals, time points and drugs as fixed effects. Moreover, an ANOVA model, which will include groups as fixed effect, will be used to examine the carry-over effect. In addition, a linear regression model will be employed to assess the linear relation of FFR values between intravenous nicorandil and the intravenous adenosine.

For secondary endpoints, the number of functionally significant lesions and ECG changes will be compared between the two drugs using Fisher's exact test and changes in blood pressure (BP) and heart rate will be compared using ANOVA models.

A two-sided p value of <0.05 will be considered statistically significant and two-sided 95% CI will be calculated. The statistical analysis plan will be developed by the principal investigator and the biostatistician before

the completion of patient recruitment and fixing of data.

Trial registration

The present study was registered at the University Hospital Medical Information Network Clinical Trials Registry (number: UMIN000019309).

Informed consent

All participants will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and about alternative therapeutic choices, using an informed consent form approved by the Institutional Review Board. The participants will be given ample time and opportunity to ask questions and to consider participation in the trial. The informed consent form signed by the participant will be required for enrolment in the trial. The investigators will maintain the original and a copy of the signed consent form with the trial records.

Confidentiality

To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial.

DISCUSSION

To induce maximal hyperaemia during FFR measurement, intravenous administration of adenosine is currently considered the gold standard method. However, adenosine infusion cannot be used for patients with contraindications such as allergy to adenosine, or severe obstructive pulmonary disease. In addition, some side effects of adenosine, such as dyspnoea, flushing, chest pain, and atrioventricular block, have been reported.⁸ Therefore, in some situations an alternative hyperaemic agent would be required or preferable to optimise FFR measurement.

Nicorandil, administered either intravenously or intracoronarily, has been shown to produce the increase in blood flow, and has a potential to be applicable for FFR measurement.^{9–21} In fact, recent studies have demonstrated the usefulness of IC administration of nicorandil for FFR measurement.^{22–24} However, there are several concerns regarding the method. FFR measurement using IC nicorandil may be suboptimal in cases of ostial coronary lesions in which disengagement of the guide catheter is mandatory to avoid pressure damping, and IC administration of hyperaemic agents with certainty is technically challenging in such lesions. Moreover, there is a possible risk of inducing arrhythmia by IC administration of nicorandil.²⁵ In addition the duration of hyperaemia after IC administration of nicorandil is around 30 s, which is sometimes not long enough to perform a pressure pullback recording for assessing the potential severity of serial stenosis in the same coronary artery, especially when a slow pullback is required.

Intravenous administration of nicorandil (0.1–0.2 mg/kg) has been shown to decrease coronary vascular resistance (by 24–53%), resulting in an increase in coronary blood flow (by 26–93%).²¹ Furthermore, it has been approved in Japan for the treatment of heart failure (at a dose of 0.2 mg/kg bolus intravenous injection followed by continuous intravenous infusion) or unstable angina, and has also become widespread in clinical use in Asian countries, as well as in Europe. A safety concern of intravenous nicorandil injection is its effect on BP. However, several studies showed that nicorandil did not decrease systolic BP (SBP) significantly in patients with low to normal SBP, while it did decrease SBP remarkably in patients with an elevated baseline SBP.^{14 26 27} Therefore, single bolus intravenous injection of nicorandil can be used safely, possibly provide a longer duration of hyperaemia compared with IC nicorandil,²⁸ and be hopefully useful for FFR measurement.

To the best of our knowledge, this crossover randomised trial is the first to investigate the efficacy of intravenous nicorandil for FFR measurement in comparison with intravenous adenosine. If this study shows the feasibility of using intravenous nicorandil as a hyperaemic method, it can serve as a platform for further evaluation in a larger population, eventually providing the alternative method for hyperaemic induction.

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Contributors TN designed the original concept. All coauthors contributed significantly to the conception and design of the study, with specific additional contributions from each coauthor within their area of expertise. The protocol was written by TN, HK and KN and it was critically reviewed by KS, TN, YF, HH and YK. All authors gave approval for the publication.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The protocol was approved by the Institutional Review Board at Chiba University Hospital (approval number: G27020) and the study is being conducted in accordance with GCP standards and ethics guidelines for clinical studies according to the Declaration of Helsinki.

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