Effect of Intracoronary Nicorandil Administration on Preventing No-Reflow/Slow Flow Phenomenon During Rotational Atherectomy

Akiyoshi Tsubokawa, MD; Kinzo Ueda, MD; Hiroki Sakamoto, MD;
Tomoyuki Iwase, MD; Shun-ichi Tamaki, MD

A major limitation of the rotational atherectomy (RA) procedure is the occurrence of the no-reflow/slow flow phenomenon and the optimal strategy is still evolving. Recent clinical studies have demonstrated the beneficial effects of nicorandil, an adenosine triphosphate (ATP)-sensitive potassium channel opener, on no-reflow in patients with acute myocardial infarction. The purpose of this study was to evaluate the effect of nicorandil on no-reflow/slow flow phenomenon during RA procedures. Sixty-one patients who underwent RA of complex coronary lesions were randomly divided into 2 groups: (i) nicorandil cocktail (n=24 patients, 37 lesions) and (ii) verapamil cocktail (n=37 patients, 63 lesions). In each group, the drug cocktail mixed with pressurized saline was infused through the 4Fr Teflon sheath of the rotablator system during the RA procedure. In the nicorandil group, the drug cocktail consisted of 24 mg of nicorandil, 5 mg of nitroglycerin, and 10,000 U of heparin. In the verapamil group, the drug cocktail consisted of 10 mg of verapamil, 5 mg of nitroglycerin, and 10,000 U of heparin. Baseline and procedure characteristics did not differ between the 2 groups. RA was performed successfully, and death, Q-wave myocardial infarction, or emergency coronary artery bypass surgery did not occur in any patients. The no-reflow/slow flow phenomenon was observed in 11/63 (17.4%) lesions of the verapamil group, but in only 1/37 (2.7%) lesions of the nicorandil group ($p=0.03$). No untoward complications were observed during nicorandil infusion. These data indicate that the intracoronary continuous infusion of nicorandil during RA procedures is easy and safe, and prevents no-reflow/slow flow phenomenon more effectively than infusion of verapamil. (*Circ J* 2002; 66: 1119–1123)

Key Words: No-reflow/slow flow phenomenon; Potassium channel opener; Rotational atherectomy

Recently, rotational atherectomy (RA) has become widely used for the treatment of complex coronary lesions that are unsuitable for balloon angioplasty or stents, including calcified, diffusely diseased lesions and small caliber vessels.^{1–4} However, several studies have shown that RA is associated with higher rates of the no-reflow/slow flow phenomenon than other coronary revascularization devices,^{5,6} and this phenomenon can lead to serious ischemic complications, such as conduction disturbances, myocardial infarction, cardiogenic shock or death.⁷ Therefore, methods involving a drug perfusion cocktail are being used to decrease the occurrence of the no-reflow/slow flow phenomenon and several clinical studies report that an intracoronary infusion of verapamil, nitroglycerin and heparin during RA procedures might be beneficial, with an incidence of no-reflow/slow flow ranging from 7 to 15.7%.^{8,9} However, the optimal strategy is still evolving.

Nicorandil [N-(2-hydroxyethyl)-nicotinamide nitrate; Chugai, Tokyo, Japan] is currently used clinically as an anti-anginal drug. This agent has been shown to have pharmacological hybrid properties as a nitrate and an adenosine triphosphate (ATP)-sensitive potassium channel-opener.¹⁰

Recently, several studies demonstrated that intravenous or intracoronary administration of nicorandil, in conjunction with coronary reperfusion, can reduce the no-reflow phenomenon in patients with acute myocardial infarction. Although the mechanism of this beneficial effect is not yet fully understood, a reduction in microvascular resistance by nicorandil seems to play a major role.^{11,12} Therefore, because the no-reflow/slow flow phenomenon during RA procedures is also caused by increased microvascular resistance,^{13,14} nicorandil may be more useful for preventing this phenomenon than verapamil. Thus, we assessed the effect of nicorandil on the no-reflow/slow flow phenomenon during RA procedures in comparison with verapamil.

Methods

Patient Population

A total of 61 consecutive patients scheduled for RA of more than one segment in a native coronary artery in the presence of stable angina pectoris symptoms and/or objective signs of ischemia were prospectively studied. Acute myocardial infarction, or the presence of an angiographically visible coronary thrombus, was the criterion for exclusion from the study. Patients with prior coronary artery bypass grafting (CABG) were not excluded. A total of 100 coronary lesions were included in the eligible cohort. Informed written consent to undergo the procedure was obtained from all patients.

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Department of Cardiovascular Medicine, Takeda General Hospital, Kyoto, Japan

Mailing address: Kinzo Ueda, MD, Department of Cardiovascular Medicine, Takeda General Hospital, Higashishiokoji-cho, Shimogyo-ku, Kyoto 600-8558, Japan. E-mail: takedadr@mbox.kyoto-inet.or.jp

Randomization

Just before the RA procedure, patients were randomized into 2 groups administered either nicorandil or verapamil, initially 1:2, but later 1:1 for each group because the number of patients who were allocated to the nicorandil group was insufficient to compare with the verapamil group. In each group, the drug cocktail was mixed in 1 L of normal saline solution and infused through the 4Fr Teflon sheath of the rotablator system (Boston Scientific Corporation, Redmond, WA, USA) at 300 mmHg during the RA procedure. In the nicorandil group, the drug cocktail consisted of 24 mg of nicorandil, 5 mg of nitroglycerin, and 10,000 U of heparin, and in the verapamil group, it comprised 10 mg of verapamil, 5 mg of nitroglycerin, and 10,000 U of heparin. A glycoprotein IIb/IIIa antagonist was not used during the RA procedure in either group because it was not available in Japan. All other protocols were the same and the operator was unaware of each patient's group assignment.

Rotational Atherectomy Procedure

All patients were premedicated at least 24 h before the procedure with aspirin (81 mg/day), nitrate, and calcium-channel blockers, but α -adrenergic blocking agents were not given. RA was performed using the standard techniques and the rotablator system. All patients received 10,000 U of intravenous heparin at the beginning of the procedure. Before the RA procedure, if possible, an intravascular ultrasound examination was performed at the operator's discretion. A 0.009-inch guide-wire was advanced across the lesion in the target vessel and positioned well distal to the lesion. The burr was slowly advanced across the lesion, using gentle forward pressure with a rotational speed of 160,000–180,000 rpm. A stepped burr technique with 0.25–0.5-mm increments was used, maintaining a burr-to-artery ratio between 0.6 and 0.85. Care was taken to minimize rpm decreases during each rotablator run, and to avoid long passes. After angiographic assessment of the procedural result, adjunctive balloon angioplasty and stent implantation were performed at the operator's discretion. After stent implantation, ticlopidine (200 mg/day) was administered for at least 1 month. Serum markers of myocardial injury were not routinely measured after the procedure in the absence of persistent chest discomfort or hemodynamic changes or dynamic ECG changes.

Follow-up

Follow-up coronary angiography was performed 3 months after the procedure, but was performed earlier if

symptoms occurred before the scheduled session.

Angiographic Analysis and Definition

The angiograms were re-read by an experienced angiographer who had not participated in the invasive procedure and was unaware of the drug cocktail regimen received by each patient. All pre-procedural, post-procedural and follow-up angiography was performed immediately after the administration of 0.2 mg of intracoronary nitroglycerin. At least 2 views of the lesion were taken and off-line quantitative coronary analysis (QCA) of the view revealing the highest degree of stenosis was performed. Lesion length, reference diameter (RD), minimal lumen diameter (MLD), and percent diameter stenosis (%DS) were calculated using a Cardiovascular Measurement System (CMS, MEDIS; Medical Imaging Systems, Nuenen, the Netherlands).

Angiographic success was defined as the achievement of a residual diameter stenosis <50%, and clinical success was defined as angiographic success combined with the absence of major complications, including Q-wave myocardial infarction, emergency CABG or death. No-reflow was defined as the cessation of flow into the distal coronary artery in the absence of a clear angiographic explanation of impaired flow (dissection, thrombus) immediately post-ablation pass. Slow flow was defined as the diminution of coronary flow by 1–2 TIMI grades from the baseline antegrade flow in the absence of a clear angiographic explanation of impaired flow (dissection, thrombus) immediately post-ablation pass. Angiographic restenosis was defined as %DS >50%, and target lesion revascularization (TLR) was defined as repeat coronary angioplasty or CABG performed for restenosis.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Comparisons were made by Student's *t* test, and categorical values by chi-square test. A *p* < 0.05 was considered significant.

Results

Baseline Characteristics (Table 1)

Twenty four patients were randomized to the nicorandil group, and 37 to the verapamil group. There was no significant difference between the 2 groups with respect to age, sex distribution, prevalence of previous myocardial infarction, number of diseased vessels, or coronary risk factors.

Baseline Angiographic Characteristics (Table 2)

There were 37 lesions in the nicorandil group and 63 in

Table 1 Baseline Patient Characteristics

	Nicorandil (n=24)	Verapamil (n=37)	<i>p</i> value
Age (years)	66 $\pm$ 10	69 $\pm$ 11	0.28
Male gender	19 (79.2)	30 (81.1)	0.85
Previous myocardial infarction	16 (66.7)	21 (56.8)	0.44
No. diseased vessels			
Single vessel	10 (41.7)	17 (45.9)	0.70
Multivessel	14 (58.3)	20 (54.1)	
Coronary risk factors			
Diabetes	7 (29.2)	16 (43.2)	0.27
Hypertension	14 (58.3)	24 (64.9)	0.61
Hyperlipidemia	14 (58.3)	14 (37.8)	0.12
Active + former smoker	6 (25.0)	12 (32.4)	0.53

Numbers in brackets are %.

Table 2 Lesion Characteristics

	Nicorandil (n=37)	Verapamil (n=63)	<i>p</i> value
Target vessel			
LAD	17 (45.9)	40 (63.5)	0.09
RCA	9 (24.3)	10 (15.9)	0.30
LCX	11 (29.7)	13 (20.6)	0.30
ACC/AHA classification			
A or B1	16 (43.2)	25 (39.7)	0.73
B2 or C	21 (56.8)	38 (60.3)	
Reference vessel diameter (mm)	2.24 $\pm$ 0.53	2.32 $\pm$ 0.48	0.44
Lesion length (mm)	13.4 $\pm$ 7.8	12.1 $\pm$ 8.6	0.45
Angiographic calcification	23 (62.2)	38 (60.3)	0.86

Numbers in brackets are %. LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Table 3 Procedural Characteristics

	Nicorandil (n=37)	Verapamil (n=63)	p value
No. of burrs/lesion	1.7±0.6	1.7±0.5	NS
Final burr size (mm)	1.63±0.29	1.77±0.31	0.03
Final burr/artery ratio	0.74±0.15	0.77±0.25	0.46
Max. ablation time (s)	36.9±6.8	34.2±7.1	0.07
Total ablation time (s)	180±75	165±93	0.47

Table 4 Initial Results and QCA Data

	Nicorandil (n=37)	Verapamil (n=63)	p value
Lesion success	36/37 (97.3)	63/63 (100)	0.19
Clinical success	23/24 (95.8)	37/37 (100)	0.21
MLD (mm)			
Pre	0.63±0.36	0.63±0.33	NS
Post	1.87±0.60	2.02±0.52	0.19
% DS			
Pre	72.1±14.4	72.8±14.2	0.19
Post	22.4±12.7	16.6±15.6	0.06

MLD, minimal lumen diameter; %DS, percent diameter stenosis.

Table 5 Angiographic Complications

	Nicorandil (n=37)	Verapamil (n=63)	p value
Acute reclosure post RA	1 (2.7)	3 (4.8)	0.61
No-reflow/slow flow	1 (2.7)	11 (17.4)	0.03
Side branch occlusion	2 (5.4)	5 (7.9)	0.66
Coronary perforation	1 (2.7)	1 (1.6)	0.70

Numbers in brackets are %. RA, rotational atherectomy.

the verapamil group. There was no significant difference between the 2 groups in the location of target vessels, the American College of Cardiology/American Heart Association type of lesions, reference vessel diameter or lesion length.

Procedural Characteristics (Table 3)

The final burr size was slightly larger in the verapamil group, but for the final burr-to-artery ratio, the maximum ablation time and the total ablation time, there was no significant difference between the 2 groups.

Initial Results and Angiographic Results by QCA

In the nicorandil group, angiographic success was achieved in 36 of 37 lesions (97.3%), and clinical success in 23 of 24 patients (95.8%). Because of a highly calcified stenosis, one lesion was unsuccessfully treated with RA. The MLD increased from 0.63 mm to 1.87 mm and the % DS decreased from 72.1% to 22.4% after the procedure.

In the verapamil group, angiographic success was achieved in 63 of 63 lesions (100%), and clinical success in 37 of 37 patients (100%). The MLD increased from 0.63 mm to 2.02 mm and the %DS decreased from 72.8% to 16.6% after the procedure. There was no significant difference between the 2 groups (Table 4).

Angiographic Complications

Frequencies of abrupt coronary reclosure, side branch occlusion and coronary perforation were comparable between the 2 groups. However, the no-reflow/slow flow

Table 6 Procedural Complications

	Nicorandil (n=24)	Verapamil (n=37)	p value
Hypotension	6 (25.0)	14 (37.8)	0.30
Bradycardia	7 (29.2)	12 (35.1)	0.79
Q wave infarction	0	0	NS
Emergency CABG	0	0	NS
Death	0	0	NS

Numbers in brackets are %. CABG, coronary artery bypass grafting.

Table 7 Restenosis and TLR at 3 Months After RA Procedure

	Nicorandil (n=37)	Verapamil (n=63)	p value
Restenosis rate	32.1%	42.8%	0.34
TLR rate	25.0%	21.4%	0.71

TLR, target lesion revascularization; RA, rotational atherectomy.

phenomenon was observed in 11/63 (17.4%) lesions of the verapamil group, but in only 1/37 (2.7%) lesions of the nicorandil group (p=0.03). Nicorandil reduced the incidence of the no-reflow/slow flow phenomenon (Table 5).

Procedural Complications

There were no major adverse cardiac events in either group. During RA procedures, there was slightly more hypotension requiring vasopressors and bradycardia in the verapamil group, but no significant difference between the 2 groups. No arrhythmias, such as accelerated idioventricular rhythm, ventricular tachycardia, or ventricular fibrillation, were associated with either protocol (Table 6).

Angiographic Restenosis and Target Lesion Revascularization

The overall lesion restenosis rate at 3 months was 32.1% in the nicorandil group and 42.8% in the verapamil group, and the TLR rates at 3 months were 25.0% and 21.4%, respectively. There was no significant difference between the 2 groups (Table 7).

Discussion

Rotational atherectomy has a unique mechanism of action based on selective ablation and pulverization of hard and calcific atherosclerotic plaque by a high-speed rotating elliptical diamond coated burr^{15,16}. During ablation of the plaque, microparticles are produced by the advancing burr and although experimental studies suggest that these particles pass harmlessly through the distal microcirculation,^{17,18} the no-reflow/slow flow phenomenon occurs in 6–15% of patients in clinical studies of RA.^{5,13,19} It is therefore important to establish clinically the treatment of the no-reflow/slow flow phenomenon, but to date, there are no uniform strategies for managing this phenomenon. In the present study, we showed that the continuous intracoronary infusion of nicorandil during RA procedures was easy, safe and more effective in preventing the no-reflow/slow flow phenomenon than verapamil.

Mechanisms for the Beneficial Effect of Nicorandil

One of the mechanisms by which nicorandil reduces the incidence of the no-reflow/slow flow phenomenon is thought to be its effect on the ATP-sensitive potassium channels.

The exact mechanism of the no-reflow/slow flow phenomenon during RA procedures has not been completely defined, but increased microvascular resistance by aggregated platelets, activated neutrophils, microembolization of the debris generated via lesion debulking and microvascular spasm seem to play a critical role.^{11,20} Therefore, nicorandil, by opening of the ATP-sensitive potassium channels, may decrease microvascular resistance, leading to an increase in myocardial blood flow. Indeed, experimental and clinical studies have demonstrated that nicorandil dilates the coronary resistance arteries more strongly than nitroglycerine.^{21–23} Another mechanism may be that nicorandil attenuates platelet aggregation and neutrophil adhesion;^{24–26} because interstitial edema, cell swelling, and capillary plugging by aggregated platelets and activated neutrophils contribute to a progressive increase in microvascular resistance, this effect may attenuate microvascular resistance, and thereby increase myocardial blood flow. Because verapamil does not attenuate the activity of neutrophils, the superior efficacy of nicorandil over verapamil observed in this study may be related to this effect of nicorandil.²⁷

Recently, Hanna et al reported that intracoronary administration of adenosine, which improves coronary microvascular circulation in a similar manner to nicorandil, reduced the incidence of the no-reflow phenomenon during RA procedures.¹³ However, when compared with adenosine, nicorandil has several advantages. First, nicorandil also dilates epicardial coronary arteries, and this effect can relieve refractory coronary spasm for which nitrates are not fully effective.^{28,29} Second, nicorandil has a longer half-life than adenosine, which has a half-life in human blood of less than 1 s and that may be too short to maintain its effects during RA. Third, adenosine induces coronary steal and negative inotropic effects, which may be detrimental in patients with ischemic heart disease. Therefore, we believe that nicorandil is a more useful agent than adenosine for inhibiting the no-reflow/slow flow phenomenon during RA procedures.

Safety of Intracoronary Continuous Infusion of Nicorandil

Nicorandil, by opening the ATP-sensitive potassium channels, causes hyperpolarization and reduces the duration of the action potential and the effective refractory period, which, in theory, might increase arrhythmias such as accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation.³⁰ However, these undesirable rhythm disorders have not as yet been demonstrated in clinical usage. None of these arrhythmias were observed during the present study. Therefore, we consider that the continuous intracoronary infusion of nicorandil during RA procedures is safe and well tolerated.

Study Limitations

First, the optimal dose and protocol of nicorandil have not been clarified in this study. Previous clinical studies with acute myocardial infarction have demonstrated that a single bolus intracoronary administration of nicorandil or peripheral intravenous continuous infusion of nicorandil can reduce the no-reflow phenomenon,^{11,12} so those protocols also may be useful in RA. Second, because many of the lesions treated in this study were severely calcified, very small, and diffuse, intravascular ultrasound was carried out in only a minority of cases. Therefore, the volume of ablated plaque, which may play a critical role of no-reflow/slow flow, was not calculated and may have influenced the

results. However, in a scintigraphic study using Tc-99m-sestamibi, Koch et al demonstrated that myocardial hypoperfusion during RA was not influenced by the volume of ablated plaque.³¹ This issue requires additional study using intravascular ultrasound examination. Third, because creatine kinase (CK) and CK-MB were not routinely measured, we did not detect a beneficial effect of nicorandil on myocardial injury. However, we consider the no-reflow/slow flow phenomenon during RA procedures, for which we could demonstrate a beneficial effect of nicorandil, to be the primary event leading to definitive myocardial injury. In addition, several experimental and clinical studies have demonstrated that nicorandil has cardioprotective effects against ischemic injury.^{11,12,32,33} Therefore, we believe that administration of nicorandil during RA procedures also has beneficial effects on myocardial injury.

Conclusions

The results here show that administration of nicorandil during RA procedures reduces the incidence of the no-reflow/slow flow phenomenon. This agent promises to be a useful adjunctive therapy for protecting the heart against ischemic injury during RA.

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