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Usefulness of intracoronary administration of fasudil, a selective Rho-kinase inhibitor, for PCI-related refractory myocardial ischemia

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ABSTRACT

Background: Intra-procedural myocardial ischemia as an iatrogenic complication still remains a critical issue in contemporary interventional cardiology. The aim of this study was to examine the usefulness of fasudil, a selective Rho-kinase inhibitor, for percutaneous coronary intervention (PCI)-related myocardial ischemia.
Methods: Among 448 PCI sessions performed between October 2015 and December 2017, we retrospectively examined 36 patients (69.0 ± 9.1 [SD] yrs., M/F 26/10) who underwent intracoronary administration of fasudil during a procedure to resolve myocardial ischemia that was resistant to intracoronary nitrate administration.
Results: The refractory myocardial ischemia was caused by distal embolization (69%), enhanced vasoconstriction at distal site of chronic total occlusion (11%), coronary spasm (11%), and coronary dissection (8%), most of which occurred immediately after balloon or stent dilatation. Intracoronary fasudil significantly improved corrected TIMI frame count (from 37 [30–56] to 24 [12–36]) and TIMI flow grade (from 2 [1–2.5] to 3 [2-3]) (both $P < 0.001$). Finally, 86% of all subjects successfully obtained TIMI flow grade 3 at the end of the procedure. Intracoronary fasudil tended to be more effective in patients with an attenuated plaque detected by intravascular ultrasound. Importantly, among the 19 elective cases, fasudil successfully prevented 17 patients from developing post-procedure myocardial infarction. Although fasudil-induced transient hypotension requiring a vasopressor was noted in 22% of the subjects, no other adverse effects were noted.
Conclusions: These results indicate that fasudil is a useful and safe therapeutic option for PCI-related myocardial ischemia refractory intracoronary nitrate.

1. Introduction

Percutaneous coronary intervention (PCI) is widely used as an effective therapeutic strategy for coronary artery disease [1,2]. Although severe acute complications related to PCI are rare in the current era, microvascular obstruction due to embolization of atheromatous materials, refractory epicardial and microvascular spasm, coronary dissection, and side brunch occlusion could cause myocardial ischemia and subsequent myocardial necrosis [3]. Especially during primary PCI for acute coronary syndrome (ACS) cases, we sometimes experience no/slow-flow phenomenon that is associated with microvascular impairment and increased risk for future adverse cardiac events [4–6]. Furthermore, in elective PCI cases, based on the 4th universal definition of myocardial infarction [7], peri-procedural myocardial infarction is noted in 7.0% and myocardial injury in 21.6% [8]. Importantly, elevated cardiac enzymes following elective PCI is also known to be associated with poor long-term prognosis [8,9]. Thus, it is important to restore sufficient myocardial blood flow not only at epicardial coronary arteries but also in coronary microcirculation as soon as possible when the PCI-related myocardial ischemia develops. Although the possible usefulness of some drugs has been proposed for this purpose [10–13], none of them has become an established therapy, and thus more effective therapy remains to be developed.

We have previously demonstrated that Rho-kinase plays an important role in the pathogenesis of coronary spasm and that fasudil, a selective Rho-kinase inhibitor, suppresses not only epicardial coronary spasm but also microvascular spasm [14–16]. Moreover, there is a case report which presented the efficacy of fasudil on the refractory coronary spasm after stent deployment [17]. In the present study, we retrospectively assessed the efficacy and safety of fasudil for the management of PCI-related myocardial ischemia refractory to intracoronary nitrates.

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Table 1
Patient characteristics (N = 36).

Age, *yrs*	69.0 ± 9.1
Male / Female, *N*	26 / 10
BMI	24.3 ± 3.9
HT, *N (%)*	24 (67)
DM, *N (%)*	16 (44)
DL, *N (%)*	26 (72)
Smoking, *N (%)*	
Current smoker	9 (25)
Ex-smoker	14 (39)
Non-smoker	13 (36)
SBP, *mmHg*	130.0 ± 22.7
DBP, *mmHg*	71.0 ± 11.8
LDL-C, *mg/dl*	89.0 ± 30.0
HbA1c, *%*	6.1 (5.7–7.1)
eGFR, *ml/min/1.73m²*	60.8 ± 13.6
BNP, *pg/ml*	43.2 (24.4–139.2)
LVEF, *%*	57.1 ± 14.4
ACS, *N (%)*	17 (47)
STEMI	9 (25)
NSTEMI	3 (8)
uAP	5 (14)
Stable AP, *N (%)*	19 (53)
CTO	5 (14)
Target vessels, *N (%)*	
LAD	20 (56)
LCX	4 (11)
RCA	12 (33)
Medications, *N (%)*	
Aspirin	36 (100)
Loading	11 (31)
P2Y12–I	36 (100)
Loading	13 (36)
β-blocker	15 (42)
ACE-I or ARB	22 (61)
Nitrate/Nicorandil	11 (31)
CCB	20 (56)
Statin	26 (72)

Results are expressed as mean ± SD or median (IQR).
ACE-I, angiotensin-converting enzyme-inhibitor; ACS, acute coronary syndrome; AP, angina pectoris; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CTO, chronic total occlusion; DPB, diastolic blood pressure; DL, dyslipidemia; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HT, hypertension; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; P2Y12–I, P2Y12-inhibitor; RCA, right coronary artery; SBP, systolic blood pressure; STEMI, ST elevation myocardial infarction; uAP, unstable angina pectoris.

Table 2
Procedural characteristics.

Aspiration, *N (%)*	10 (32)
Balloon dilation, *N (%)*	36 (100)
Rotablation, *N (%)*	3 (8)
Stent use, *N (%)*	28 (78)
DES, *N (%)*	21 (58)
BMS, *N (%)*	7 (19)
Number of stent / target vessel, *N*	1.0 (1.0–2.0)
Stent diameter, *mm*	3.0 (3.0–3.5)
Stent length / target vessel, *mm*	37.0 (28–47)
DCB, *N (%)*	4 (11)
POBA, *N (%)*	4 (11)
IABP use, *N (%)*	3 (8)
IVUS analysis, *N*	29
Plaque morphology, *N (%)*	
Arc of attenuation 180–360	17 (59)
Attenuation length >5 mm	19 (66)
Attenuation plaque	15 (52)
Fasudil administration, *N*	36
Dose of fasudil, *mg*	18.0 (12–30)
Reasons for fasudil administration, *N (%)*	
Distal embolization	25 (70)
Enhanced vasoconstriction at the distal site of CTO	4 (11)
Epicardial spasm	4 (11)
Dissection	3 (8)
Timing of fasudil administration, *N (%)*	
After aspiration	2 (6)
After rotablation	2 (6)
After balloon dilatation	15 (42)
After stent deployment	17 (47)
Temporary hypotension requiring vasopressor, *N (%)*	8 (22)

Results are expressed as median (IQR).
BMS, bare metal stent; CTO, chronic total occlusion; DCB, drug-coating balloon; DES, drug-eluting stent; IABP, intra-aortic balloon pumping; IVUS, intravascular ultrasound; POBA, plain old balloon angioplasty.

2. Methods

2.1. Study population

Among a total of 448 PCI sessions performed from October 2015 to December 2017, we performed intracoronary administration of fasudil in 36 patients during PCI procedure after their consent in order to resolve unexpected and prolonged myocardial ischemia refractory to enough dose of intracoronary nitrate. Since fasudil is licensed for the prevention of ischemic stroke complicated with cerebral vasospasm after subarachnoid hemorrhage as a treatment covered by public insurance in Japan, we used the drug off-label. The situation in which we needed intracoronary fasudil included ACS in 17 cases (9 with ST-segment elevation myocardial infarction (STEMI), 3 with non-STEMI, and 5 with unstable angina) and elective PCI in 19 cases. In the present study, PCI-related myocardial ischemia was defined as complications that developed during PCI procedure, including new-onset of chest pain due to myocardial ischemia, obvious coronary slow flow by angiogram, or ischemic ECG changes such as sustained ST-segment elevation/depression of more than 0.1 mV or new appearance of a negative U-wave in at least 2 related leads [18,19]. As a general PCI procedure, aspirin (100 mg/day) plus clopidogrel (75 mg/day) or prasgrel (3.75 mg/day) with the approved doses in Japan were given in advance of PCI procedure [20]. All subjects received bolus unfractionated heparin to maintain an activated clotting time over 300 s throughout PCI procedure. Glycoprotein IIb/IIIa inhibitors were unavailable in Japan. PCI strategies were left to the discretion of each treating physician. Intracoronary administration of fasudil was carefully performed from a guiding catheter directly or through a microcatheter for 1–5 min with the monitoring of arterial blood pressure and ECG. A median dosage of fasudil we used was 18.0 (IQR: 12–30) mg.

2.2. Angiographic analysis

Coronary angiography was performed with a frame rate of 10/sec. Distal embolization was defined as visible occlusion at distal coronary artery, no/slow-flow phenomenon, and angiographically unexplained ischemic symptom and ECG changes [18,19]. If coronary dissection was suspected, it was confirmed with an intracoronary imaging device. Thrombolysis in Myocardial Infarction (TIMI) flow grade and corrected TIMI frame count (CTFC), which is the number of cine frames for the attainment of contrast to the distal landmark in the left anterior descending coronary artery (LAD) divided by 1.7, was evaluated as described previously [21,22]. In the present study, when CTFC was uncountable due to TIMI flow grade 0 or 1, their CTFC was defined as 100 [23].

2.3. IVUS analysis

Intravascular ultrasound (IVUS) scans were performed using one of the following mechanical sector scanners, including Atlantis SR Pro2 or Opticross 6 (Boston scientific, Boston, Massachusetts, USA), View It, Navifocus, or Alta View (Terumo Medical Corp, Tokyo, Japan), and a motorized transducer pull back system (1.0 mm/s). Quantitative IVUS measurements with planimetry software (QIvus 3.0, Medis Medical Imaging System, Leiden, The Netherlands) were performed as

previously described [24]. Attenuated plaque, which has been reported as a predictor of no/slow-flow phenomenon, was defined as ultrasound attenuation with more than 180° and 5 mm length [23].

2.4. Cardiac enzyme analysis

Peripheral blood samples were obtained on admission and the day after PCI procedure. In elective PCI cases, serum levels of CK-MB were compared between baseline and post-PCI. PCI-related myocardial infarction was defined as more than 3 times greater than the upper limit of normal CK-MB level [25].

2.5. Statistical analysis

Parametric and non-parametric data were presented as mean± standard deviations (SD) or median with interquartile range (IQR), respectively. Student t-test for normal distribution and Mann-Whitney *U* test for asymmetric distribution were used to compare continuous variables. Paired data were compared using paired *t*-test or Wilcoxon signed rank test. McNemar test was used to compare the ratio of TIMI flow grade 3. A P-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS statistics software 24 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

Baseline characteristics of the 36 patients with PCI-related myocardial ischemia refractory to intracoronary nitrate are shown in Table 1. Mean age was 69.0 years and 72.2% of them were male. The most frequent target vessel of PCI was the LAD. PCI procedures are summarized in Table 2. All patients underwent coronary dilatation with a balloon at least once during a procedure, and subsequent stent deployment was performed in 28 patients (78%). In those, median diameter and total-length of deployed stents were 3.0 mm (IQR: 3.0–3.5) and 37.0 (IQR: 28.0–47.0) mm, respectively. Intracoronary thrombus aspiration was performed in 10 patients and no patient underwent distal protection. Three patients with cardiogenic shock needed mechanical circulatory support with intra-aortic balloon pumping.

3.2. Efficacy and safety of fasudil for PCI-related myocardial ischemia

In the present study, refractory myocardial ischemia was caused by distal embolization (69%), enhanced vasoconstriction at the distal site of chronic total occlusion (11%), coronary spasm (11%), and coronary dissection (8%), most of which occurred immediately after balloon or stent dilatation (Table 2). Fig. 1 shows the representative images of the therapeutic effect of fasudil on slow-flow phenomenon in a patient with ACS. Intracoronary fasudil significantly decreased CTFC (from 37 [IQR: 30–56] to 24 [IQR: 12–36]) and improved TIMI flow grade (from 2 [IQR: 1–2.5] to 3 [IQR: 2–3]) (both $P < 0.001$) (Fig. 2A and B). Fasudil exerted a rapid effect on the improvement of coronary flow, which lasted over time. Finally, 86% of the patients (76% of ACS and 95% of elective PCI cases) achieved TIMI flow grade 3 in the target vessel. Among the 29 patients who underwent IVUS examinations, attenuated plaque was detected in 52% of them (Table 2). CTFC before intracoronary administration of fasudil tended to be greater in patients with attenuated plaque as compared with those without it (42 [IQR:

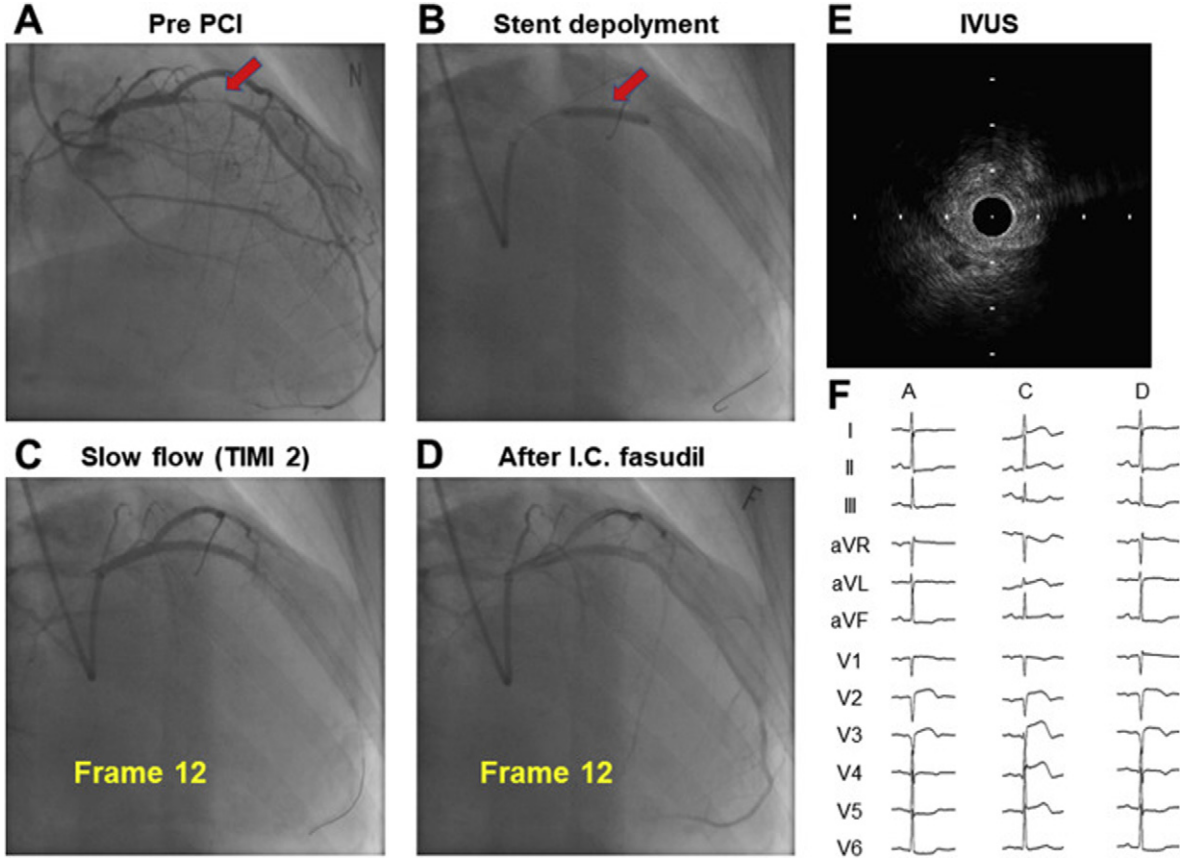

Fig. 1. Fasudil ameliorated slow-flow phenomenon in a patient with ACS. (**A**) Coronary angiogram showed 90% stenosis at the proximal segment of the LAD (red arrow) as a culprit lesion in a patient with ACS. (**B**) Everolimus-eluting stent (Synergy® 3.0 × 20mm) was placed at the lesion (red arrow). (**C**) Slow-flow phenomenon refractory to intracoronary nitrate developed after stent deployment. (**D**) Intracoronary fasudil promptly improved the coronary flow. (**E**) Attenuated plaque was observed by IVUS imaging. (**F**) ST-segment elevation in I, aVL, V3-5 leads developed after the stent deployment, which was resolved after intracoronary fasudil administration.

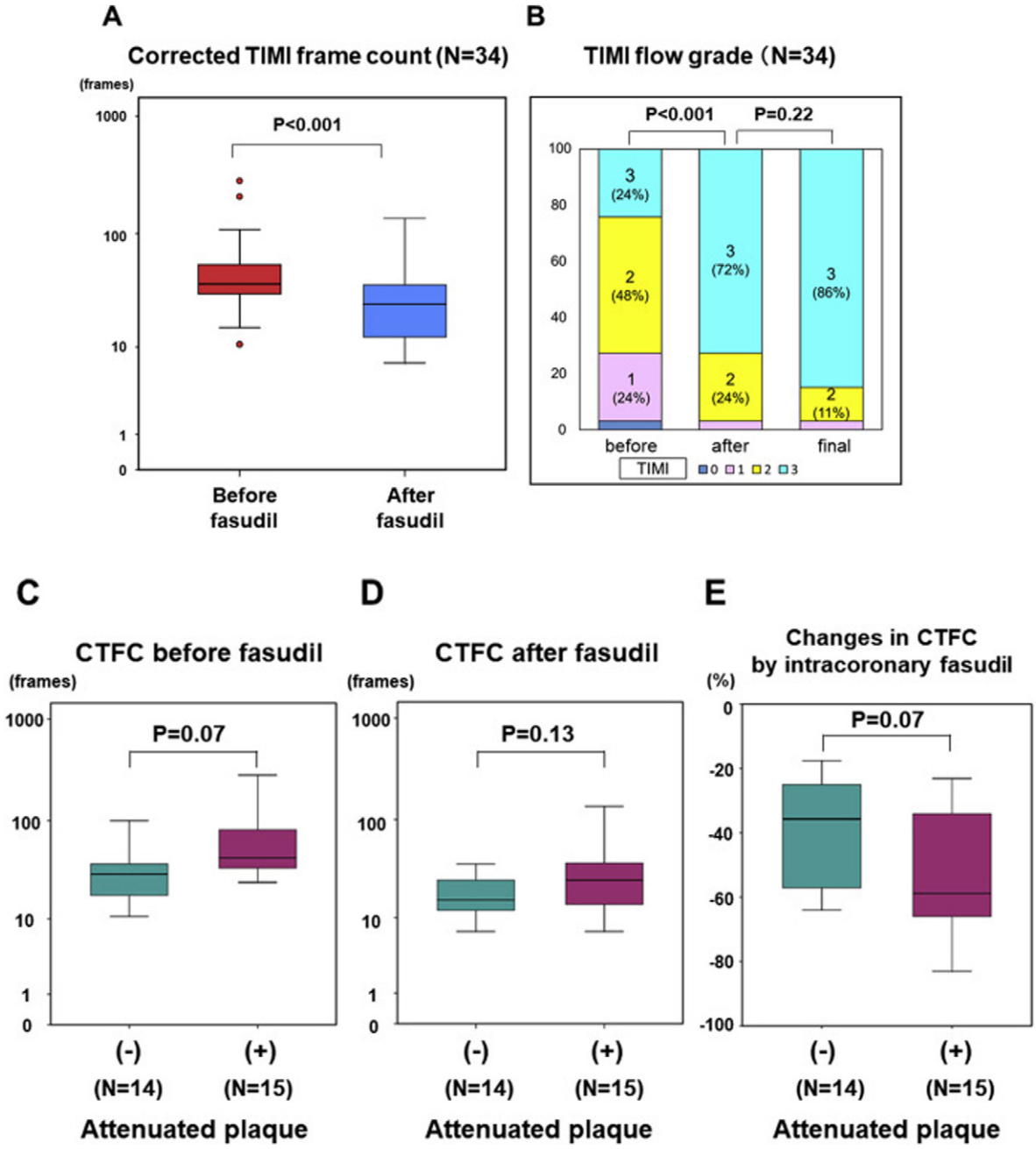

Fig. 2. Fasudil improves corrected TIMI frame count and TIMI flow grade. (**A**) Fasudil significantly reduced CTFC after intracoronary administration (N = 34). Results are expressed as box-and-whisker plots; the central box covers the interquartile range, with the median indicated by the line within box. The whiskers extend to the most extreme values within 1.5 interquartile ranges. More extreme values are plotted indivisually. (**B**) Fasudil significantly and promptly improved TIMI flow grade and remained effective until the end of the PCI procedure. The achievement rate of TIMI flow grade 3 was 86% at the final angiography. TIMI, Thrombolysis in Myocardial Infarction. (**C**) Before fasudil use, CTFC tended to be higher in patients with attenuated plaque (N = 15) than in those without it (N = 14). (**D**) After intracoronary fasudil administration, CTFC became comparable between the 2 groups. (**E**) % Changes in CTFC were greater in patients with attenuated plaque (N = 15) than in those without it (N = 14). Results are expressed as box-and-whisker plots; the central box covers the interquartile range with the median indicated by the line within box.

34–100] vs. 29 [IQR: 18–37], P = 0.07), whereas that after fasudil was comparable between the 2 groups (25 [IQR: 12–45] vs. 15 [IQR: 12–25], P = 0.13) (Fig. 2C and D). Percent changes in CTFC after fasudil also tended to be greater in the former than in the latter (P = 0.07) (Fig. 2E). Among the elective PCI cases (n = 19), although CK-MB levels tended to be increased slightly after PCI procedure with fasudil (from 6.0 [IQR: 4.0–8.0] to 7.0 [IQR: 5.0–13.0] U/L, P = 0.08), about 90% of the patients were able to avoid the development of peri-procedural myocardial infarction. Regarding adverse effects, fasudil significantly and transiently decreased systolic blood pressure (from 129 ± 23 to 108 ± 20 mmHg, P < 0.001). A temporary use of vasopressors, such as etilefrine and noradrenaline, was required in 22% of the subjects with no subsequent complications (Table 2).

4. Discussion

In the present study, we were able to demonstrate that (1) fasudil, a selective Rho-kinase inhibitor, significantly improved CTFC and TIMI flow grade in patients with PCI-related myocardial ischemia refractory to intracoronary nitrate, (2) fasudil could prevent the occurrence of PCI-related myocardial infarction in elective PCI cases, (3) although transient hypotension to intracoronary fasudil occurred in 20% of

patients, there was no other serious adverse side-effects. To the best of our knowledge, this is the first study that demonstrates the efficacy and safety of fasudil as a novel therapeutic option for PCI-related myocardial ischemia refractory to intracoronary nitrate.

4.1. Efficacy and safety of fasudil for PCI-related refractory myocardial ischemia

It has been reported that biomarkers levels for myocardial necrosis are frequently elevated after PCI despite angiographically successful results [26]. Such peri-procedural myocardial injury is caused by prolonged ischemia due to side brunch occlusion, distal embolization, coronary spasm, enhanced vasoconstriction at the distal site of chronic total occlusion (CTO), and coronary dissection [3,8]. Those complications depend on not only patient-related factors but also lesion and/or procedural complexities [27–30]. Additionally, iatrogenic plaque rupture that is inevitable for PCI procedure could cause embolization of coronary circulation with plaque debris and/or thrombus, the release and activation of vasoactive inflammatory peptides and enhanced vasoconstricting reactivity in both epicardial and microvascular coronary arteries [3,31]. Indeed, it has been reported that vasomotor dysfunction other than organic occlusion in coronary microvessels could be responsible for impaired coronary blood flow and prolonged myocardial ischemia in slow/no-flow phenomenon [3,6,10,11]. Likewise, despite successful reperfusion of a chronic total occlusion (CTO) lesion, distal site is often vasoconstricting and shows a hyperconstricting response to stent deployment. We and others demonstrated that fasudil is useful for the treatment of refractory coronary spasm at the stent edges and the distal site of opened CTO lesion [17,32,33]. We also demonstrated that inhibition of Rho-kinase with fasudil ameliorates acetylcholine-induced coronary spasm not only in the epicardial but also in microvascular coronary arteries [15,16]. Furthermore, in the canine ischemia/reperfusion model, hydroxyfasudil, a metabolite of fasudil, was able to induce coronary vasodilatation in both small coronary arteries and arterioles, leading to the increase in coronary blood flow in a dose-dependent manner [34]. Those findings indicate that fasudil could be a potent therapeutic option for coronary functional disorders, including coronary no/slow-flow phenomenon. Indeed, in the present study, improvement of CTFC after intracoronary fasudil tended to be greater in patients with attenuated plaque than in those without it, which has been regarded as a predictor of no/slow-flow phenomenon. Thus, fasudil may have an ability to prevent PCI-related refractory myocardial ischemia that could cause myocardial infarction. The incidence of PCI-related myocardial infarction of the present study was 11%, a comparable incidence in the previous study [31], although our patients with refractory myocardial ischemia were at higher risk of developing myocardial infarction. Although several vasodilating agents were examined for the treatment of no/slow-flow phenomenon during the last 2 decades, most of them were administered in a preventive protocol before PCI procedure [10,11]. Thus, the present findings have clinical significance, as we were able to demonstrate the usefulness of fasudil for PCI-related refractory myocardial ischemia in a treatment protocol [14–16]. Regarding the adverse effects of fasudil, it caused hypotension in 22% of the patients, which were controlled with vasopressor agents, indicating the acceptable safety of the Rho-kinase inhibitor.

4.2. Limitations

Several limitations should be mentioned for the present study. First, the present study was a single-center, retrospective, and a single arm study with a relatively small sample size. Second, in the present study, the causes of PCI-related myocardial ischemia were heterogeneous. However, more than 90% of the patients had coronary hyperconstrictive responses, such as epicardial coronary spasm and distal embolization, all of which were ameliorated by fasudil. Third, we did not examine the long-term outcomes of the patients. Fourth, we did not directly compare the effect of fasudil with those of vasodilator drugs. Fifth, in the present study, we defined peri-procedural myocardial infarction as more than 3 times greater than the upper limit of normal CK-MB level, as we had no data of serum levels of troponin levels after PCI. In the current universal definition of myocardial infarction, PCI-related myocardial infarction is defined as more than 5 times elevation of cardiac troponin levels than the 99th percentile of the upper reference limit [7]. Thus, we might have underestimated the incidence of PCI-related myocardial infarction in the present study.

4.3. Conclusions

Intracoronary administration of fasudil is an effective and safe strategy for patients with PCI-related myocardial ischemia refractory to intracoronary nitrates.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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