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ORIGINAL ARTICLE

Effect of intracoronary thrombectomy on 30-day mortality in non-diabetic patients with acute hyperglycemia after acute myocardial infarction

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KEYWORDS
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Summary
Background: There is limited evidence about useful therapeutic interventions for patients with acute hyperglycemia (AH) after acute myocardial infarction (AMI).
Methods: We studied 2433 consecutive non-diabetic AMI patients who underwent percutaneous coronary intervention (PCI) within 24 h after the onset. Patients were divided into two groups according to the presence or absence of AH (admission serum glucose level $\geq$11.1 mmol/l). We assessed the association between intracoronary thrombectomy and the clinical outcome in AMI patients with AH.
Results: Patients with AH had more risk factors than those without AH. The 30-day mortality rate of patients with AH was significantly higher than that of those without (11.7% vs 1.7%, $p < 0.001$). Among patients with AH, the 30-day mortality rate was significantly lower for those with intracoronary thrombectomy than those without it (4.9% vs 17.2%, $p = 0.004$). Among patients without AH, however, the 30-day mortality rate was similar between those with and without intracoronary thrombectomy (1.5% vs 1.9%, p = NS). Multivariate analysis showed that intracoronary thrombectomy was associated with an improved 30-day mortality rate for patients with AH (hazard ratio: HR 0.184, 95% CI 0.057—0.598, $p = 0.005$).

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Conclusions: In AMI patients with AH, intracoronary thrombectomy prior to PCI might improve the 30-day mortality rate.

Introduction

On admission for acute myocardial infarction (AMI), acute hyperglycemia (AH) is often observed in non-diabetic patients as well as in diabetic patients [1,2]. Several studies have found an association between AH in non-diabetic patients and an adverse clinical outcome after AMI [3—8], suggesting that AH may represent either stress hyperglycemia due to a large infarct or cardiogenic shock [5,6,9], or be secondary to pre-existing or undiagnosed diabetes [1,4]. It has been reported that AH might cause microvascular damage [10] or increase coagulability [11,12], resulting in the no-reflow phenomenon that might induce more extensive myocardial damage and impair left ventricular function [7,13].

Despite the adverse clinical impact of AH [5,6], there are limited data about interventions that may have a beneficial effect in patients with AH after AMI. On the other hand, it has been reported that performing intracoronary thrombectomy before percutaneous coronary intervention (PCI) might improve coronary perfusion, salvage more myocardium, and reduce mortality in patients with AMI, especially in those with diabetes or at high risk [14—19]. Therefore, we examined the hypothesis that intracoronary thrombectomy improves the clinical outcome after AMI in patients with AH by reviewing the database of the Osaka Acute Coronary Insufficiency Study (OACIS) registry.

Methods

Study population

Patients were identified in the OACIS registry. A detailed description of the OACIS has been published elsewhere [20—22]. Briefly, the OACIS is a prospective multicenter observational study, in which 25 participating hospitals from the Osaka region of Japan record demographic, procedural, and outcome data, and collect blood samples from patients with AMI. The study protocol was approved by each hospital's ethical committee and written informed consent was provided by each patient at the time of registration. The registry is designed to collect uniform prospective data on AMI patients that can be used to assess clinical variables, therapeutic procedures, and clinical events. The diagnosis of AMI required 2 of the following 3 criteria: (1) a history of central chest pressure, pain, or tightness lasting for 30 min or more; (2) ST-segment elevation greater than 0.1 mV in at least 1 limb lead or 2 precordial leads; and (3) an increase in the serum creatine kinase (CK) concentration to more than twice the upper limit of normal. All patients presenting within 1 week after the onset of AMI were registered prospectively as soon as a diagnosis of AMI was made.

Among 8025 consecutive AMI patients registered in the OACIS between April 1998 and December 2007, 4597 patients who fulfilled the following criteria were enrolled in the present study: (1) coronary angiography and coronary intervention performed within 24 h after the onset of AMI; and (2) the plasma glucose level and glycated hemoglobin (HbA_{1c}) level were measured on admission. To minimize the influence of pre-existing diabetes mellitus (DM) on hyperglycemia, we excluded patients who had been diagnosed as having DM or were on treatment for DM (diet, tablets, or insulin) and patients with an admission HbA_{1c} >5.8%. A total of 2433 patients fulfilled the criteria. These patients were divided into 2 groups according to whether they had a plasma glucose $\geq$ 11.1 mmol/l on admission (AH group: $N = 231$) or not (non-AH group: $N = 2202$). We also divided the AH and non-AH groups into subgroups according to whether or not intracoronary thrombectomy was done before PCI. Hypertension was defined as a history of systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or antihypertensive therapy. Hyperlipidemia was defined as fasting total cholesterol $\geq$220 mg/dl, fasting triglycerides $\geq$150 mg/dl, or antilipidemic therapy. Smoking was defined as currently or previously smoking. Before hospital discharge (mean 14 days after the onset), 2011 patients underwent echocardiography at each hospital. The following variables were measured: end-diastolic dimension (Dd) and end-systolic dimension (Ds).

Coronary angiography and PCI

Informed consent for cardiac catheterization and PCI was obtained from all patients at each hospital. Coronary angiography was performed immediately

Table 1 Clinical, angiographic characteristics and major medications during hospitalization of the study population according to absence/presence of acute hyperglycemia with and without intracoronary thrombectomy.

Variables	Non-AH group, ICT			AH group, ICT			AH vs non-AH
	No ($N = 1218$)	Yes ($N = 984$)	*p*-Value	No ($N = 128$)	Yes ($N = 103$)	*p*-value	*p*-Value
Clinical characteristics							
Men	76.4%	78.8%	0.200	72.7%	68.9%	0.562	0.033
Age (yrs)	65.6 ± 11.8	64.0 ± 12.4	0.099	68.7 ± 11.9	68.0 ± 11.8	0.671	<0.001
Body mass index (kg/m^2)	23.4 ± 3.4	23.7 ± 3.3	0.364	22.5 ± 3.1	22.7 ± 3.4	0.306	<0.001
Hypertension	55.3%	52.3%	0.183	52.3%	50.5%	0.793	0.489
Hyperlipidemia	42.6%	40.7%	0.362	31.3%	30.1%	0.887	0.001
Smoker	62.8%	67.0%	0.044	54.7%	53.4%	0.895	0.002
History of myocardial infarction	10.9%	11.0%	1.000	10.2%	5.8%	0.336	0.220
History of angina	22.0%	21.7%	0.917	24.2%	20.4%	0.529	0.803
ST elevation myocardial infarction	85.8%	90.3%	0.001	87.5%	94.2%	0.114	0.285
Killip classification > I	12.9%	11.4%	0.295	40.6%	34.0%	0.340	<0.001
Killip classification = IV	2.5%	2.3%	0.274	20.3%	21.4%	0.404	<0.001
Time from symptom onset to admission (h)	2.50(1.17—6.50)	2.33(1.00—5.65)	0.032	1.92(1.00—4.18)	1.70(0.93—2.67)	0.147	<0.001
Glycated hemoglobin A1c (%)	5.15 ± 0.3	5.22 ± 0.3	0.729	5.14 ± 0.4	5.25 ± 0.4	0.837	0.742
Admission glucose levels (mmol/l)	7.27 ± 1.4	7.37 ± 1.5	0.119	14.40 ± 3.5	14.48 ± 3.6	0.872	<0.001
Angiographic characteristics							
Multivessel coronary disease	35.3%	32.9%	0.259	46.1%	36.9%	0.181	0.020
Collateral circulation	37.4%	39.9%	0.235	35.2%	37.9%	0.682	0.523
Infarction related artery							
Right coronary artery	32.7%	38.9%	<0.001	35.1%	41.7%	0.588	0.389
Left anterior descending artery	48.4%	43.8%	0.004	44.5%	46.6%	0.791	0.628
Circumflex artery	14.6%	13.6%	0.539	10.2%	3.9%	0.080	0.003
Diagonal or bypass graft	3.5%	2.8%	0.433	0.8%	1.0%	1.000	0.021
Left main coronary artery	0.8%	0.9%	0.821	9.4%	6.8%	0.631	<0.001
Initial TIMI flow grade 3	18.1%	8.1%	<0.001	16.4%	8.7%	0.115	0.840
Stent implantation	61.5%	83.3%	<0.001	69.5%	89.3%	<0.001	0.025
Medications during hospitalization							
Aspirin	99.7%	99.4%	0.357	99.2%	99.0%	1.000	0.318
ACE inhibitors or AT1 antagonists	81.4%	87.0%	<0.001	61.7%	74.8%	0.047	<0.001
Beta-blockers	42.9%	50.1%	0.001	42.2%	50.5%	0.233	1.000
Statin	37.7%	41.0%	0.124	25.0%	33.0%	0.190	0.002
Insulin or any oral antidiabetics	1.8%	1.2%	0.283	2.3%	0%	0.498	1.000

AH, acute hyperglycemia; ICT, intracoronary thrombectomy; ACE, angiotensin-converting enzyme; AT, angiotensin.

after admission. Coronary artery stenosis was considered to be clinically significant if the luminal diameter was reduced by ≥75%. The presence of collaterals supplying the infarct-related artery was assessed by observing whether opacification occurred from a site distal to the culprit lesion on coronary angiography. Patients underwent PCI according to current guidelines with a conventional catheter-based system. Perfusion of the infarct-related artery was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) study classification [23], and the final TIMI flow grade was determined from the final angiograms. Among the patients receiving intracoronary thrombectomy, a RESCUE catheter (Boston Scientific Scimed, Inc., Maple Grove, MN, USA), a Thrombuster catheter (Kaneka Medix Corp., Osaka, Japan), a TVAC catheter (Nipro, Osaka, Japan), and an Export aspiration catheter (PercuSurge System, Medtronic AVE, Danvers, MA, USA) were used in 33.9%, 54.9%, 3.9%, and 7.3% of the patients, respectively.

Statistical analysis

The clinical end-point for this study was all-cause mortality after AMI. Results are expressed as the mean ± SD or median with 25th and 75th percentiles for continuous variables, while qualitative data are presented as numbers or percentages. Differences of continuous variables between groups were compared by Student's *t*-test, while categorical variables were compared by the chi-square test. Survival curves were constructed by the Kaplan–Meier method and the significance of differences in survival were assessed by the log-rank test. A multiple logistic regression model was used to assess whether intracoronary thrombectomy was independently associated with an improved 30-day mortality. The variables included in this model were age, male sex, body mass index (BMI), hypertension, hyperlipidemia, smoking, history of myocardial infarction, history of angina, ST elevation myocardial infarction, Killip class >I, the time from symptom onset to admission, angiographic findings (multivessel disease, collateral circulation, and initial TIMI grade flow), and performance of stenting. Analysis of data was performed by using SPSS statistical software (version 11.0, SPSS Japan Inc., Tokyo, Japan). For all analyses, statistical significance was defined as $p < 0.05$.

Results

Intracoronary thrombectomy was performed in 103 patients (44.6%) among the 231 patients with AH, and in 984 patients (44.7%) among the 2202 patients without AH. The clinical and angiographic characteristics, as well as major medications during hospitalization, are listed in Table 1 for the four subgroups. Patients with AH were older and more often female than those without AH. The prevalence of classic risk factors such as hyperlipidemia or smoking was lower in patients with AH, but they had a higher Killip class on admission and a shorter interval to admission from symptom onset than patients without AH. HbA_{1c} on admission did not differ between the patients with and without AH. The patients with AH more frequently had multivessel coronary disease and a culprit lesion in the left main coronary artery. Although clinical and angiographic characteristics differed between the patients with and without AH, these did not differ between the patients with and without intracoronary thrombectomy in patients with AH. Regardless of AH, among the patients treated by intracoronary thrombectomy, the percentage of patients who had a culprit lesion in the right coronary artery or underwent coronary stenting was higher, and the percentage of patients with an initial TIMI flow of

Table 2 Mortality and causes of death at day 30 according to absence/presence of acute hyperglycemia with and without intracoronary thrombectomy.

	Non-AH group, ICT			AH group, ICT		
	No (*N* = 1218)	Yes (*N* = 984)	*p*-Value	No (*N* = 128)	Yes (*N* = 103)	*p*-Value
All cause death	1.9%	1.5%	0.622	17.2%	4.9%	0.004
Cardiac death	1.7%	1.4%	0.611	16.4%	4.9%	0.006
Heart failure	1.2%	0.8%	0.521	11.7%	4.9%	0.098
Re-infarction	0%	0%		1.6%	0%	0.504
Mechanical complication	0.2%	0.4%	0.707	2.3%	0%	0.256
Arrhythmia	0.2%	0.2%	1.000	0.8%	0%	1.000
Other cardiac death	0.1%	0%	1.000	0%	0%	
Non-cardiac death	0.2%	0.1%	1.000	0.8%	0%	1.000

grade 3 was lower than those without intracoronary thrombectomy. The percentage of patients being treated with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and statins was higher among those without AH. Few patients started insulin or oral antidiabetic agents during hospitalization.

There were 65 deaths at day 30 in the present study. Mortality and causes of death are shown in Table 2. The 30-day mortality rate of patients with AH was significantly higher than that of those without it (11.7% vs 1.7%, $p < 0.001$). Among the patients without AH, the 30-day mortality rate was similar between those with and without intracoronary thrombectomy (1.5% vs 1.9%, p = NS). Among the patients with AH, however, the 30-day mortality rate of those with intracoronary thrombectomy was significantly lower than that of those without intracoronary thrombectomy (4.9% vs 17.2%, $p = 0.004$). The difference in the Kaplan—Meier estimate was significant by the log-rank test ($p = 0.001$) (Fig. 1). Univariate analysis revealed a beneficial effect of intracoronary thrombectomy on the 30-day mortality of patients with AH [hazard ratio (HR) 0.266, 95% CI 0.101—0.701, $p = 0.007$], whereas intracoronary thrombectomy did not show a beneficial effect for patients without AH (HR 0.804, 95% CI 0.419—1.541, $p = 0.511$). Because there were differences in baseline clinical and angiographic characteristics among the 4 subgroups, we also assessed the beneficial effect of intracoronary thrombectomy on 30-day mortality by multivariate analysis. After adjustment for clinical and angiographic characteristics,

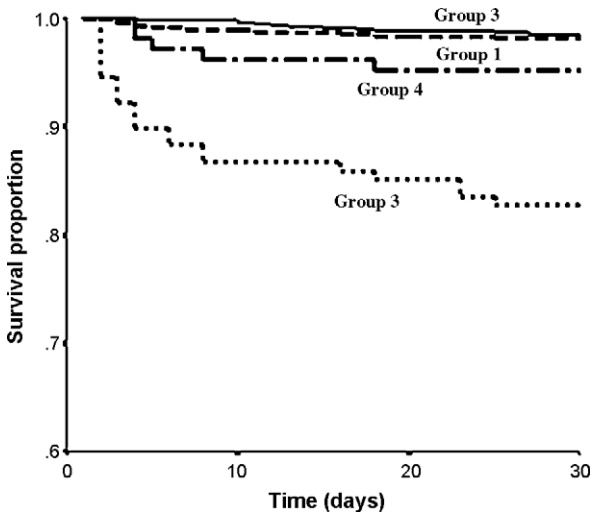

Figure 1 Kaplan—Meier estimates of survival after AMI according to study groups (log-rank test for all comparisons, $p < 0.001$). Group 1 indicates patients without acute hyperglycemia treated without intracoronary thrombectomy; Group 2, patients without acute hyperglycemia treated with intracoronary thrombectomy; Group 3, patients with acute hyperglycemia treated without intracoronary thrombectomy; Group 4, patients with acute hyperglycemia treated with intracoronary thrombectomy. The 30-day mortality rate in patients with acute hyperglycemia treated with intracoronary thrombectomy (Group 4) was improved toward similar level of patients without acute hyperglycemia.

Table 3 Univariate and multivariate analysis for 30-day mortality after AMI.

30-Day death	Non-AH group			AH group		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Univariate						
Age	1.071	1.038—1.104	<0.001	1.058	1.020—1.097	0.002
Male	0.812	0.394—1.672	0.572	0.665	0.304—1.452	0.306
BMI	0.990	0.892—1.098	0.846	0.920	0.806—1.051	0.219
Killip class > I	4.757	2.482—9.117	<0.001	3.501	1.573—7.793	0.002
Multivessel disease	1.732	0.916—3.275	0.091	4.270	1.805—10.10	0.001
Intracoronary thrombectomy	0.804	0.419—1.541	0.511	0.266	0.101—0.701	0.007
Multivariate						
Age	1.033	0.989—1.079	0.147	1.055	0.994—1.119	0.076
Male	1.121	0.401—3.129	0.828	0.819	0.215—3.110	0.769
BMI	0.969	0.848—1.108	0.645	1.027	0.851—1.240	0.780
Killip class > I	4.994	2.084—11.70	<0.001	1.758	0.541—5.706	0.348
Multivessel disease	1.210	0.492—2.977	0.679	4.365	1.170—16.28	0.028
Intracoronary thrombectomy	1.185	0.486—2.887	0.709	0.184	0.057—0.598	0.005

AH, acute hyperglycemia; CI, confidence interval. The variables included in the model were age, male gender, body mass index (BMI), hypertension, hyperlipidemia, smoking, a history of myocardial infarction, a history of angina, ST-elevation myocardial infarction, Killip class > I, time from symptom onset to admission, angiographic findings (including multivessel disease, collateral circulation, and initial TIMI grade flow), use of intracoronary thrombectomy, and use of stenting.

Table 4 The incidence of final TIMI flow grade 3, the peak CK, and echocardiographic variables according to absence/presence of acute hyperglycemia with and without intracoronary thrombectomy.

	Non-AH group, ICT			AH group, ICT		
	No ($N=1218$)	Yes ($N=984$)	p-Value	No ($N=128$)	Yes ($N=103$)	p-Value
Final TIMI flow grade 3	88.7%	90.3%	0.210	82.8%	90.3%	0.126
Peak CK (IU/l)	2663 ± 2590	2959 ± 2341	0.006	5252 ± 4974	4655 ± 3342	0.300
Echocardiography	($N=958$)	($N=876$)		($N=88$)	($N=89$)	
End-diastolic dimension (mm)	50.4 ± 6.2	50.3 ± 5.9	0.782	52.4 ± 6.8	49.4 ± 5.4	0.001
End-systolic dimension (mm)	34.9 ± 10.4	35.7 ± 15.7	0.201	37.2 ± 9.1	35.3 ± 7.2	0.128

CK, creatine kinase.

its beneficial effect remained significant among patients with AH (HR 0.184, 95% CI 0.057—0.598, $p=0.005$) (Table 3). On the other hand, a beneficial effect of intracoronary thrombectomy on 30-day mortality was not seen in patients without AH.

There was a non-significant increase in the incidence of final TIMI flow grade 3 (90.3% vs 82.8%, $p=0.126$) and non-significant decrease in peak CK (4655 ± 3342 IU/l vs 5252 ± 4974 IU/l, $p=0.300$) between AH patients with and without intracoronary thrombectomy. Furthermore, the end-diastolic dimension assessed by echocardiography at chronic phase after AMI was significantly smaller in patients undergoing intracoronary thrombectomy than in those without it (49.4 ± 5.4 mm vs 52.4 ± 6.8 mm, $p=0.001$) (Table 4).

Discussion

Considerable attention has been focused on the acute treatment of patients with AMI and AH [24—26]. To our knowledge, this is the first study to demonstrate an association between intracoronary thrombectomy before PCI and improved 30-day mortality of non-diabetic patients with AH after AMI.

Although it is difficult to determine the mechanisms leading to the efficacy of intracoronary thrombectomy, there are several possible explanations. In this study, mortality due to cardiac causes and/or heart failure was lower in AH patients with intracoronary thrombectomy than in those without (Table 2). So, it may be suggested intracoronary thrombectomy might prevent or improve heart failure due to left ventricular remodeling after AMI and reduce cardiac death. Left ventricular remodeling has been recognized as a major predictor of heart failure and cardiovascular death after AMI [27—29], and a recent study by Bauters et al., showed that stress hyperglycemia was an independent predictor of left ventricular remodeling after the first anterior myocardial infarction in non-diabetic patients [30]. Previous studies have suggested that AH could be associated with more extensive infarction [6,31]. In this study, there was non-significant decrease in peak CK between AH patients with and without intracoronary thrombectomy. Furthermore, the end-diastolic dimension assessed by echocardiography at chronic phase after AMI was significantly smaller in patients undergoing intracoronary thrombectomy than in those without it (Table 4), suggesting that intracoronary thrombectomy might reduce left ventricular remodeling in AH patients. It will be necessary to confirm whether intracoronary thrombectomy reduces left ventricular remodeling by further investigation.

Intracoronary thrombectomy might also prevent or improve the no-reflow phenomenon. Iwakura et al. reported that AH was associated with no-reflow on contrast echocardiography [13]. Ishihara et al. reported that angiographic no-reflow occurred more frequently in patients with AH and they suggested that impaired microvascular function might contribute to this outcome [7]. The no-reflow phenomenon is a predictor of infarct size and an adverse outcome after AMI [32,33]. Although the prevalence of the no-reflow phenomenon was not assessed in this study, there was a tendency to increase the incidence of final TIMI flow grade 3 in AH patients with intracoronary thrombectomy (Table 4). It has been also reported that intracoronary thrombectomy reduces the occurrence of the no-reflow phenomenon [34], so it is possible that intracoronary thrombectomy reduced the no-reflow phenomenon and hence improved the prognosis of patients with AH.

In this study, some AH patients may have been undiagnosed diabetics who fitted the criteria for DM. Buell et al investigated the diagnosis of diabetes in 4935 patients and found that an HbA_{1c} of 5.8% yielded the highest sensitivity (86%) and specificity (92%) in their study population [35]. Therefore, we used an HbA_{1c} of 5.8% as the cut-off value to exclude diabetes. However, several recent studies have shown that abnormal glucose

tolerance diagnosed by the oral glucose tolerance test (OGTT) might be common in AMI patients with undiagnosed diabetes [36—38]. Thus, an OGTT is necessary to completely exclude diabetes. In this study, we did not obtain OGTT data, but we routinely measured HbA_{1c} at admission. As shown in Table 1, few patients were newly treated with insulin or oral antidiabetic agents, suggesting that our subjects might not include enough potential diabetics to change the results. Because it has been reported that an HbA_{1c} of 5.2% completely excludes diabetes [39], we also assessed the subjects who had HbA_{1c} levels of 5.2% or lower. The number of patients was too small for multivariate analysis, but we obtained the same results as in the full study population by univariate analysis (data not shown).

Limitations

This study had several limitations. First, we did not assess the number of aspiration procedures or the total thrombus burden that was removed. Second, it was an observational study and was not randomized. This means that several baseline clinical and angiographic characteristics differed among our four subgroups, and there may have been potential confounding factors even after adjustment for these differences in baseline clinical and angiographic characteristics. However, our subjects reflected the 'real world' population because they were typical unselected AMI patients who received PCI early after symptom onset and admission to a high-volume hospital in a large city.

Conclusion

Our findings suggest that non-diabetic patients who show acute hyperglycemia after AMI have a markedly better outcome when intracoronary thrombectomy is done with PCI.

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