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ORIGINAL ARTICLE

Prevention of contrast-induced nephropathy by chronic pravastatin treatment in patients with cardiovascular disease and renal insufficiency

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Summary
Background: Contrast-induced nephropathy (CIN) is known to increase morbidity and mortality of cardiovascular disease. Recent studies have shown statins prevented CIN after contrast media exposure, but optimal statin type and dosage are still unknown.
Purpose: The aims of the present study were to evaluate whether chronic pravastatin treatment before scheduled coronary angiography or percutaneous coronary intervention could reduce the incidence of CIN and to elucidate the factors related to CIN in patients with renal insufficiency.
Methods: We studied 431 consecutive patients with renal insufficiency. One hundred ninety-four patients were receiving pravastatin treatment as standard chronic treatment of hypercholesterolemia. Serum creatinine levels were measured at baseline (pre-procedure) and within 48 h after contrast media exposure (peak post-procedure). CIN was defined as an increase in the serum creatinine values of $\geq$25% or $\geq$0.5 mg/dl after contrast media exposure. Logistic regression analysis was performed to evaluate the important factors related to CIN using four variables: age, pravastatin, pre-procedure serum creatinine, and contrast volume.
Results: CIN was observed in 36 patients (8.4%). Patients without pravastatin ($p < 0.01$), high level pre-procedure serum creatinine ($p < 0.01$), and high contrast volume ($p = 0.034$) had a significantly higher incidence of CIN. Logistic regression analysis revealed that pravastatin treatment ($\chi^2 = 6.549$, $p = 0.011$, odds ratio = 0.34), pre-procedure serum creatinine ($\chi^2 = 6.294$, $p = 0.009$, odds

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ratio = 2.78), and contrast volume ($\chi^2 = 4.484$, $p = 0.034$, odds ratio = 1.01) were independently related to the decreased risk of CIN.
Conclusions: Chronic pravastatin treatment before contrast media exposure was important for preventing CIN in patients with renal insufficiency. Also, reducing the dose of contrast media was important for preventing CIN in patients with high-baseline serum creatinine levels.

Introduction

Infusion of contrast media can lead to acute renal insufficiency [1]. Contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI) is known to increase morbidity and mortality in patients with cardiovascular disease. Among the baseline characteristics before contrast media exposure, preexisting renal insufficiency, diabetic mellitus, congestive heart failure, advanced age, and high-contrast volume exposure are reported to be the risk factors related to CIN [1—3]. Although the pathophysiological process of CIN is still controversial, a combination of renal circulation leading to medullary ischemic damage, oxygen free radicals inducing tubular cell alterations and parenchymal vasoconstriction are the main factors leading to CIN [4]. Pre-procedural intravenous hydration, *N*-acetylcysteine, theophylline, and usage of lower-osmolar contrast media, as adjunctive treatments during angiographic procedures, are reported to reduce the incidence of CIN in patients with renal insufficiency [5,6].

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) became widely used in patients with hypercholesterolemia, but statins also reduce the risk of cardiovascular disease, progression of nephropathy, and development of diabetes because of their pleiotropic effects including improvement in endothelial dysfunction, increased nitric oxide bioavailability, anti-oxidant effects, anti-inflammatory properties, and stabilization of atherosclerotic plaques above and beyond that of cholesterol lowering [7—10]. In addition, a recent report demonstrated that statins prevented CIN after PCI [11]. Although statins are clinically expected as a new prophylactic treatment, there are few reports regarding the prevention of CIN. From recent publications, pravastatin (10 mg/day), among several statins, reduced the rates of renal dysfunction in patients with cardiovascular disease and chronic kidney disease [12]. The aims of the present study were to evaluate whether chronic pravastatin treatment, as a standard treatment of hypercholesterolemia, before contrast media exposure, could reduce the incidence of CIN in patients with renal insufficiency, and to elucidate the factors related to CIN in patients receiving pre-procedural intravenous hydration.

Methods

Study patients

We evaluated 431 consecutive patients (367 men and 64 women, mean age 70.4 ± 8.9 years) with renal insufficiency (defined as serum creatinine level ≥1.1 mg/dl) undergoing scheduled coronary angiography or PCI between April 2002 and October 2008 at Kansai Medical University Hospital. The pre-procedure serum creatinine (baseline creatinine) was measured before the contrast media exposure and peak post-procedure serum creatinine (maximum creatinine) was measured within 48 h after the exposure (immediately after, 24 h, 48 h). CIN was defined as an increase in the serum creatinine values of ≥0.5 mg/dl or ≥25% increase within 48 h after the procedure in the absence of any other causes [13]. Creatinine clearance was calculated by applying the Cockcroft—Gault formula; ([140 − age] × kg of body weight/(mg dl) of serum creatinine × 72) with female gender adjustment (creatinine clearance × 0.85) [14]. The maximum dose of contrast media that can be safely administered was calculated according to the following formula: 5 ml/kg of body weight/(mg dl) of serum creatinine (maximum, 300 ml) [15]. All patients were hydrated with 1 ml/(kg h) of half-isotonic saline solution before and 12 h after the contrast media exposure and were monitored to avoid volume overload.

The exclusion criteria were as follows: (1) baseline pre-procedure serum creatinine level <1.1 mg/dl; (2) patients on chronic or temporary dialysis; (3) acute myocardial infarction or unstable angina within 48 h; (4) emergency coronary angiography that could not comply with our hydration protocol; (5) congestive heart failure

with low ejection fraction (<35%); (6) receiving other statin treatment. None of the patients received noradrenalin, dopamine, theophylline, or *N*-acetylcysteine in this study. Pravastatin was administered for the treatment of hypercholesterolemia (serum cholesterol >200 mg/dl) in 194 patients (45.0%). Pravastatin was started more than at least 28 days before contrast media exposure. Pravastatin dose was 10 mg/day in 192 patients and 20 mg/day in 2 patients. We defined diabetes mellitus as receiving oral medication or insulin therapy.

The patients were divided into CIN group and non-CIN group; clinical variables and pre-procedure medications were compared.

Coronary angiography and PCI

A non-ionic low-osmolality contrast media were used in all patients. The patients were given at least 3000 units of intravenous heparin and PCI was performed by conventional techniques after intravenous administration of 10,000 units of heparin. The target lesion (>75% stenosis) was successfully dilated in all patients. The local ethical committee on human research approved the study protocol and informed consent was obtained from all patients.

Statistical analysis

The results are reported as the mean ± standard deviation. Statistical analysis between the 2 groups was performed by the Student's *t* test for continuous variables and chi-square analysis or Fischer exact test for discrete variables. All calculated *p* values are 2-tailed. A *p* value <0.05 was considered significant. Logistic regression analysis using four clinical variables (age, pre-procedure serum creatinine, contrast volume, and pravastatin treatment) was performed to evaluate the important factors related to CIN.

Results

Among 431 patients with scheduled coronary angiography or PCI, the lesion was in the left anterior descending coronary artery in 264 patients, left circumflex coronary artery in 184 patients, and right coronary artery in 210 patients. One hundred fifty-six patients had 1-vessel disease and 66 patients had 3-vessel disease. The mean pre-procedure serum creatinine was 1.43 ± 0.34 mg/dl (range: 1.1—3.3 mg/dl). Three patients in the non-CIN group had major complications during coronary angiography or PCI. Coronary rupture occurred after ballooning in 1 patient, but was immediately managed by low-pressure balloon expansion. Cerebral infarction developed after coronary angiography in 1 patient and right hemiplegia lasted during hospitalization. Complete heart block occurred during PCI using rotablator in 1 patient and temporary pacemaker was inserted.

Comparisons of clinical characteristics between patients with and without pravastatin

One hundred ninety-four patients were taking pravastatin (pravastatin) and 237 patients did not have statins (no pravastatin). Comparisons of clinical characteristics between the 2 groups are shown in Table 1. There were no significant differences between the 2 groups in lipid levels; hypercholesterolemia (pravastatin 26.8% vs. no pravastatin 24.9%, $p = 0.771$), total cholesterol (183.1 ± 37.5 mg/dl vs. 181.9 ± 40.1 mg/dl, $p = 0.762$), triglycerides (156.5 ± 88.4 mg/dl vs. 141.6 ± 67.2 mg/dl, $p = 0.057$) and low density lipoprotein cholesterol (109.5 ± 37.7 mg/dl vs. 108.9 ± 37.1 mg/dl, $p = 0.868$). There were no significant differences between the 2 groups in the incidence of diabetes mellitus (20.1% vs. 26.2%, $p = 0.634$), hemoglobin A1c (6.3 ± 1.3% vs. 6.4 ± 2.1%, $p = 0.543$). Pre-procedure serum creatinine (pravastatin 1.4 ± 0.4 mg/dl vs. no pravastatin 1.4 ± 0.4 mg/dl, $p = 0.179$), creatinine clearance (41.4 ± 16.8 ml/min vs. 39 ± 17.1 ml/min, $p = 0.157$), administration of contrast volume (124.1 ± 53.8 ml vs. 123.6 ± 51.4 ml, $p = 0.915$) and incidence of patients exceeding maximal allowable contrast dose (13.4% vs. 14.3%, $p = 0.65$) were identical between the 2 groups. Patients without pravastatin had a significantly higher incidence of CIN (4.1% vs. 11.8%, $p = 0.003$).

Contrast-induced nephropathy

CIN was observed in 36 patients (8.4%). Clinical characteristics and pre-procedure medications are shown in Table 2. There were no significant differences in advanced age, sex, hemoglobin A1c, the incidence of diabetic mellitus, lipid disorder, hemoglobin, and body mass index between the 2 groups. Higher pre-procedure serum creatinine (lower creatinine clearance) and larger contrast volume usage were observed in the CIN group

Table 1 Comparison of clinical characteristics in patients with or without pravastatin.

	Pravastatin treatment		*p*-Value
	(+) $n=194$	(−) $n=237$	
Age (years)	69.9 ± 8.8	70.9 ± 8.9	0.233
Sex (male)	179 (92.3%)	188 (79.3%)	0.447
Pre-procedure serum creatinine (mg/dl)	1.4 ± 0.3	1.4 ± 0.3	0.179
Creatinine clearance (ml/min)	41.4 ± 16.8	39 ± 17.1	0.157
Diabetes mellitus (Hemoglobin A1c ≥6.5%)	39 (20.1%)	62 (26.2%)	0.634
Diabetes mellitus	48 (24.7%)	73 (30.8%)	0.602
Hemoglobin A1c (%)	6.3 ± 1.3	6.4 ± 2.1	0.543
Hypercholesterolemia (>200 mg/dl)	52 (26.8%)	59 (24.9%)	0.771
Total cholesterol (mg/dl)	183.1 ± 37.5	181.9 ± 40.1	0.762
Triglycerides (mg/dl)	156.5 ± 88.4	141.6 ± 67.2	0.057
Low density lipoprotein cholesterol (mg/dl)	109.5 ± 37.7	108.9 ± 37.1	0.868
Hemoglobin (g/dl)	12.3 ± 2.0	12.1 ± 2.0	0.184
Body mass index (%)	24.2 ± 3.5	23.7 ± 3.7	0.199
Contrast volume (ml)	124.1 ± 53.8	123.6 ± 51.4	0.915
Exceeding maximal contrast dose	26 (13.4%)	34 (14.3%)	0.65
CIN	8 (4.1%)	28 (11.8%)	0.003
Clinical presentation			
Previous myocardial infarction	110 (56.7%)	96 (40.5%)	<0.001
Angina pectoris	47 (24.2%)	88 (37.1%)	0.004
Angiographic findings			
Single vessel disease	58 (29.9%)	100 (42.2%)	0.008
Three vessel disease	29 (14.9%)	37 (15.6%)	0.849
Left anterior descending artery	123 (63.4%)	141 (60.8%)	0.407
Arteriosclerosis obliterans	6 (3.1%)	13 (5.5%)	0.249
Post-coronary bypass surgery	12 (6.2%)	21 (8.9%)	0.299
PCI	99 (51.0%)	106 (44.7%)	0.083
Left ventricular ejection fraction (%)	53.9 ± 13.2	53.9 ± 15.0	0.993

CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention.

compared to the non-CIN group. The incidence of exceeding the maximal allowable contrast dose was more frequently observed in patients with CIN. Among the pre-procedure medications, only pravastatin was more frequently given in the non-CIN group than in the CIN group and a significantly lower incidence of CIN was observed in patients with pravastatin compared to those without pravastatin (47.1% vs. 22.2%, $p=0.004$) (Table 2). There were no significant differences in clinical characteristics and angiographic procedures between the 2 groups.

Logistic regression analysis

To determine the important variables related to CIN, logistic regression analysis using four variables (age, pre-procedure serum creatinine, contrast volume, and pravastatin treatment) revealed that the pre-procedure serum creatinine, contrast volume and pravastatin treatment were the independent variables related to CIN (Table 3).

Discussion

Contrast media used in diagnostic and interventional angiographic procedures can cause acute iatrogenic renal insufficiency [1]. Furthermore, deterioration of renal function within 48 h after contrast media exposure is implicated as a poor prognosis in patients with preexisting renal insufficiency [16]. The occurrence of CIN has significant short- and long-term implications for patients' outcome [2]. The number of angiographies using contrast media is increasing in clinical practice and higher doses are administered to sicker and older patients. Therefore, it is important to determine the factors related to CIN and to investigate the pre-procedural treatments to prevent CIN. The incidence of CIN in a general population has been calculated to be <2%, but the incidence of CIN has been calculated to be 20—30% in high-risk patients: patients with chronic renal insufficiency, diabetes mellitus, congestive heart failure, and advanced age [1,13]. In this study, we investigated patients with mild renal insufficiency and found that the

Table 2 Clinical characteristics and pre-procedure medication.

	CIN		*p*-Value
	(−) *n* = 395	(+) *n* = 36	
Age (years)	70.9 ± 8.9	72.9 ± 7.6	0.078
Sex (male)	339 (85.8%)	28 (77.8%)	0.341
Pre-procedure serum creatinine (mg/dl)	1.4 ± 0.3	1.6 ± 0.5	0.003
Creatinine clearance (ml/min)	40.9 ± 16.7	31.4 ± 18.3	0.001
Diabetes mellitus (Hemoglobin A1c ≥6.5%)	89 (22.5%)	12 (33.3%)	0.164
Diabetes mellitus	110 (27.8%)	11 (30.6%)	0.646
Hemoglobin A1c (%)	6.3 ± 1.8	6.4 ± 1.3	0.774
Hypercholesterolemia (>200 mg/dl)	104 (26.3%)	7 (19.4%)	0.412
Total cholesterol (mg/dl)	182.9 ± 39.1	177.7 ± 36.7	0.447
Triglycerides (mg/dl)	147.4 ± 78.3	157.9 ± 71.2	0.465
Low density lipoprotein cholesterol (mg/dl)	108.7 ± 37.2	113.5 ± 38.2	0.483
Hemoglobin (g/dl)	12.3 ± 2.0	11.6 ± 2.3	0.093
Body mass index (%)	23.9 ± 3.39	24.1 ± 5.46	0.773
Contrast volume (ml)	122.2 ± 64.1	141.8 ± 64.0	0.034
Exceeding maximal contrast dose	46 (11.6%)	14 (38.9%)	<0.001
Clinical presentation			
Previous myocardial infarction	185 (46.8%)	21 (58.3%)	0.223
Angina pectoris	127 (32.2%)	8 (22.2%)	0.263
Three vessel disease	60 (15.2%)	6 (16.7%)	0.814
Left anterior descending artery	239 (60.5%)	25 (69.4%)	0.292
Left ventricular ejection fraction (%)	54.3 ± 13.6	49.5 ± 17.4	0.193
Pre-procedure medications			
Angiotensin receptor blocker	159 (40.3%)	11 (30.6%)	0.254
Angiotensin-converting enzyme inhibitors	157 (39.7%)	17 (47.2%)	0.382
Pravastatin	186 (47.1%)	8 (22.2%)	0.004
Nicorandil	166 (42.0%)	18 (50%)	0.354
Aspirin	327 (82.8%)	30 (83.3%)	0.933
Loop diuretic	121 (30.6%)	15 (41.7%)	0.178

CIN, contrast-induced nephropathy.

incidence of CIN was 8.4%. The incidence of CIN was lower compared to other studies because we examined selected patients with stable hemodynamic condition and our patients received pre-procedural hydration with half-sonic solution to prevent CIN.

Presentation of CIN

Statins not only reduce the serum cholesterol levels, but also protect renal function in patients with advanced renal insufficiency and coronary artery disease [12] by their pleiotropic effects including anti-inflammatory and immunomodulatory [17,18], antithrombotic [19], and vascular effects [20]. Khanal et al. reported that administration of statins before PCI was associated with a lower incidence of CIN [11]. Although their findings suggested that statin therapy reduced the risk of CIN, the results remain tentative because of the heterogeneity of their patients with respect to inadequate hemodynamic states. Despite identical levels of pre-procedure serum creatinine and administration of contrast volume, we found that patients with pravastatin had significantly lower incidence of CIN compared to those without pravastatin. We demonstrated pre-procedure chronic pravastatin

Table 3 Factors related to CIN.

	Chi-square statistic	*p*-Value	Odds ratio	95% CI
Age (years)	2.068	0.150	1.03	0.99—1.08
Pre-procedure Cr (mg/dl)	6.294	0.009	2.78	1.30—5.94
Pravastatin	6.549	0.011	0.34	0.15—0.77
Contrast volume (ml)	4.484	0.034	1.01	1.00—1.01

CIN, contrast-induced nephropathy; Cr, serum creatinine.

treatment used as a standard chronic treatment of hypercholesterolemia was associated with the reduction of CIN. In this study, the patients receiving pravastatin treatment were well controlled, and there were no significant differences between the pravastatin group and the placebo group in the serum lipid levels. Besides lipid lowering effects, our findings indicated that chronic pravastatin treatment of hypercholesterolemia was important in patients with cardiovascular disease. Although the preventive mechanism of CIN by pravastatin treatment remains unknown, it is mediated via the pleiotropic actions rather than lipid lowering effects. Pravastatin (10 mg/day) was effective in reducing proteinuria mediated by inhibiting renal endothelin-1 synthesis [21]. Moreover pravastatin may be more beneficial for renal protection than other statins, because of its water-soluble structure. Standard doses (10—20 mg/day) of pravastatin without any adverse affect on organs (insulin secretion from the pancreatic β cells, sugar uptake by fat cells or muscles) are reported to be effective in preventing coronary artery disease [22—25]. Desirable the pleiotropic actions of water-soluble statins, pravastatin was beneficial for the prevention of CIN.

Risk factors for CIN

Although diabetes mellitus is one of the risk factors of CIN in patients with renal insufficiency [1], there were no significant differences in hemoglobin A1c level and history of diabetes mellitus between the CIN and non-CIN groups in this study. There is no definitive evidence that CIN correlates with the duration of diabetes or suboptimal glycemic control, but adequate glycemic control should be achieved before contrast media exposure in diabetic patients because acute hyperglycemia can lead to direct renal damage [6,26]. Also, there is no consensus regarding the role of advanced age as a risk factor of CIN [2,6]. In this study, age was not a predictive factor for CIN by the multivariate analysis. A high prevalence of CIN in elderly patients is multifactorial in origin and may be attributable to renal arteriosclerosis or panvasculopathy [6].

Pre-procedure intravenous hydration and low contrast volume exposure reduce CIN in patients with renal insufficiency [2,7]. According to these reports, we performed routine pre-procedural volume expansion and used contrast media at minimum dosage in all patients. However, there was a significantly higher incidence of patients exceeding maximal contrast dose in the CIN group and contrast volume was found as an independent risk factor related to CIN by the multivariate analysis.

Limitations of this study

Three limitations of this study should be addressed. First, there was no randomization of pravastatin treatment in this study. However, significant risk factors for CIN such as contrast volume and pre-procedure serum creatinine were not different and we excluded the potential effect of other unknown confounders as much as possible. Also, it was difficult to evaluate whether chronic pravastatin treatment could reduce the incidence of CIN by randomization because it was predicted that there are significant differences between the 2 groups in the serum lipid levels. Second, our observational study was limited to a small sample size to elucidate the effectiveness of pravastatin on development of CIN in patients with severe renal insufficiency. Third, the appropriate duration of pre-procedure treatment and dosages of pravastatin to prevent CIN could not be clarified. Nonetheless, we provide evidence that chronic pravastatin treatment was an important prophylactic medication when associated with a low dose of contrast media and pre-procedural hydration for patients with renal insufficiency.

Conclusions

Pravastatin treatment before contrast media exposure was an important factor associated with the reduction in CIN after coronary angiography or PCI in patients with cardiovascular disease and renal insufficiency.

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