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CLINICAL RESEARCH

Contrast-Induced Nephropathy and Oxygen Pretreatment in Patients With Impaired Renal Function

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Introduction: Contrast-induced nephropathy is a complication following coronary angiography and percutaneous coronary intervention. Because contrast-induced nephropathy is a predictor of long-term mortality in patients with ischemic heart disease undergoing percutaneous coronary intervention, preventive strategies are required. We assessed the effects of periprocedural oxygenation on contrast-induced nephropathy among patients with pre-existing renal dysfunction.

Methods: A total of 200 consecutive patients with impaired renal function (estimated glomerular filtration $<$ 60 ml/min per 1.73 m^2) undergoing elective cardiovascular angiography were randomly assigned to an oxygenation treatment (n = 100) or control group (n = 100). In oxygenation treatment, pure oxygen (2 L/min) was administered for 10 minutes before exposure to contrast medium. The primary endpoint was the incidence of contrast-induced nephropathy, defined as a $\geq$ 25% increase in serum creatinine levels from baseline within 48 hours of exposure.

Results: In the oxygenation treatment group, partial pressure of arterial oxygen was higher (135 $\pm$ 25 mm Hg vs. 84 $\pm$ 10 mm Hg, $P < 0.001$); contrast-induced nephropathy incidence was lower (1% vs. 8%, odds ratio [OR] = 0.12, 95% confidence interval [CI] = 0.01–0.95, $P = 0.02$); and partial pressure of arterial carbon dioxide and bicarbonate base lactate levels were similar compared with those in the control group. Upon univariate analysis, excess and absence of oxygenation treatment (OR = 9.18, CI = 1.13–74.86, $P = 0.03$) and anemia (OR = 4.30, CI = 1.04–17.78, $P = 0.04$) were shown to be associated with contrast-induced nephropathy incidence.

Conclusion: Oxygenation, a simple, nonpharmacological strategy, may be beneficial when using contrast media in patients with impaired renal function from noninvasive angiography to emergency catheterization.

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Contrast-induced nephropathy (CIN), a complication following coronary angiography and percutaneous coronary intervention (PCI),[1] can progress to acute kidney injury and irreversible chronic kidney disease (CKD).[2] CIN has been recognized as a significant predictor of long-term mortality in patients with ischemic heart disease who are undergoing PCI.[3,4] Consequently, several preventive strategies have been developed; however, to date, only isotonic saline hydration has been accepted and applied as a standard preventive measure.[5] CIN is caused by a combination of renal ischemia and direct toxic effects of contrast media on renal tubular cells.[6] The renal medulla is uniquely susceptible to ischemic injury.[7] Contrast media may cause medullary hypoxia by shunting blood flow to the renal cortex.[8,9] Although hydration exerts a degree of protection by maintaining renal plasma flow and improving intrarenal hypoxia, hydration alone is insufficient to prevent CIN, particularly in high-risk patients.

A more effective approach toward CIN prevention may be achieved by combining isotonic saline hydration with oxygenation prior to contrast medium exposure. We recently reported the Option CIN study, showing

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that oxygenation treatment decreased CIN incidence in patients undergoing elective cardiac catheterization angiography.[10] The majority of patients enrolled in the Option CIN study had normal renal function; 122 of 349 patients (35%) had an estimated glomerular filtration rate (eGFR) < 60/ml/min/1.73 m^2. The incidence of CIN is widely recognized to be higher in patients with reduced eGFR.[11] Indeed, CIN occurred more frequently in patients with eGFR < 60 ml/min/1.73 m^2 compared to those with eGFR ≥ 60 ml/min/1.73 m^2 (6.5% vs. 0.8%, $P < 0.01$) in our previous study.[10] Moreover, renal damage from CIN is more severe in individuals with pre-existing impaired renal function than in those with normal renal function. Accordingly, we sought to determine whether oxygenation treatment is effective among patients with pre-existing renal dysfunction, who tend to have a higher incidence of CIN.

Our proposed non-pharmacological preventive strategy using oxygen is safe, cost-saving, and widely applicable in either the elective or emergency setting for both outpatients and critically ill patients. The Extended-Option CIN study, a single-center, prospective, randomized controlled study, aimed to extend our previous findings to patients with reduced eGFR, a relatively high-risk subset of CIN, who underwent cardiac catheterization using contrast media.

MATERIALS AND METHODS

Study Design

The Option CIN study was a prospective open-label, randomized, single-center study of patients who underwent scheduled cardiovascular angiography, percutaneous coronary intervention (PCI), or both (n = 349) from 29 April 2011 to 16 August 2011. The Extended-Option CIN study extended the recruitment period of the Option CIN study to evaluate the preventive effect of oxygenation on CIN in patients with impaired renal function, as a subpopulation analysis of the previous study. In the interim analysis of the previous study, 200 patients were enrolled (control group, n = 100; oxygen group, n =100). CIN occurred in 5 control-group patients and 1 treatment-group patient, all of whom demonstrated impaired renal function. Thus the rate of CIN among patients with impaired renal function was 14.7% (5 of 34) in the control group and 2.8% (1 of 36) in the treatment group. In the present study, sample size calculation was conducted based on this interim analysis using a CIN incidence of 2.8% in the oxygenation treatment group and 14.7% in the control group. To detect a difference in CIN incidence between the 2 groups using the Fisher exact probability test at a power of 80%, α error of 0.5 (2-sided), and β error of 0.05, we calculated that 89 patients per control group and treatment group would need to be enrolled. Factoring in a 10% dropout rate, we estimated that 98 patients were needed per group. Therefore, we enrolled and evaluated 200 new patients with impaired renal function in the present study.

Study Population

Between 1 September 2011 and 30 June 2012, a total of 200 consecutive patients with an eGFR < 60 ml/min/1.73 m^2 (mean, 48.4 $\pm$ 9.3 ml/min/1.73 m^2, range 18.4–59.9 ml/min/1.73 m^2) who underwent elective cardiovascular angiography, PCI, or both were enrolled. Exclusion criteria were acute coronary syndrome, end-stage renal failure requiring dialysis, cardiogenic shock, symptomatic and congestive heart failure, pregnancy, a history of hypersensitivity to contrast media, metformin ingestion within 48 hours of study entry, chronic obstructive pulmonary disease, oxygen saturation level <90% (indicating respiratory failure, necessitating a supply of oxygen), use of an antioxidant drug such as *N*-acetylcysteine to prevent CIN, severe infection, and severe malnutrition. Patients in whom CIN occurred were followed up in terms of clinical outcomes and renal function for 1 month after the procedure, with some followed up for as long as 1 year.

Study Protocol

Eligible patients were randomly assigned in a 1:1 ratio to receive either supplemental oxygen (oxygenation treatment group) or room air (control group). All patients received i.v. hydration with 0.9% isotonic saline at a rate of 1 ml/kg per hour (or 0.5 ml/kg per hour in cases with an ejection fraction $< 40\%$) for 12 hours before and after the procedure as a standard preventive measure. Randomization of patients was performed by a computer in blocks of 4. Groups were sequentially assigned by a research pharmacist who dispensed medications but was not otherwise involved in the study.

Blood oxygenation levels were assessed using arterial blood gas samples obtained before and after the procedure through an arterial sheath. Serum creatinine and blood urea nitrogen levels were measured before angiography (during hydration before contrast) and 48 hours after the procedure to determine the development of CIN. Catheterization was performed via the radial artery, or the femoral artery in difficult cases, without sedation. Low osmolality, non-ionic contrast agent iopamidol (Iopamiron, Osaka, Japan) was used. The eGFR was calculated using a level-modified Japanese adaptation of the Modification of Diet in Renal Disease formula[12]: eGFR in men $= 0.741 \times 175 \times$ (age in years) $^{-0.203} \times$ (serum creatinine in mg/dl) $^{-1.154}$,