International Journal of Cardiology 195 (2015) 228–234

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Continuous intravenous infusion of nicorandil for 4 hours before and 24 hours after percutaneous coronary intervention protects against contrast-induced nephropathy in patients with poor renal function

Takahide Nawa, Kazuhiko Nishigaki *, Yujiro Kinomura, Toshiki Tanaka, Yoshihisa Yamada, Masanori Kawasaki, Shinya Minatoguchi

Department of Cardiology, Respirology, and Nephrology, Gifu University Graduate School of Medicine, Gifu, Japan

ARTICLE INFO

Article history:
Received 27 December 2014
Received in revised form 27 April 2015
Accepted 14 May 2015
Available online 22 May 2015

Keywords:
Contrast-induced nephropathy
Randomized trial
Nicorandil
Prognosis

ABSTRACT

Background: We conducted a prospective randomized trial to assess the protective effect of continuous intravenous infusion of nicorandil against contrast-induced nephropathy (CIN) in patients with poor renal function.
Methods and results: We randomly assigned 213 patients who would subsequently undergo elective percutaneous coronary intervention (PCI) and who had a high serum cystatin C level to a saline group (n = 107) or a nicorandil group (n = 106, nicorandil infused in addition to saline for 4 h before and 24 h after PCI). There were no significant differences in baseline characteristics between the two groups. However, the average percent increases in serum creatinine and cystatin C following PCI were significantly smaller in the nicorandil group than the saline group. Likewise, the average percent decline in the estimated glomerular filtration rate was smaller in the nicorandil group. Correspondingly, the incidence of CIN was dramatically lower in the nicorandil group than the saline group (2.0% vs. 10.7%, $p < 0.02$). Univariate regression analysis revealed nicorandil treatment to be the only significant predictor of CIN development (odds ratio: 0.173, 95% confidence interval: 0.037–0.812, $p = 0.026$).
Conclusions: Nicorandil strongly prevents CIN in patients with poor renal function undergoing PCI.

1. Introduction

Contrast-induced nephropathy (CIN) is a serious complication that occurs after radiographic examination using iodinated radiocontrast medium, and that has become a significant source of hospital morbidity and mortality due to the ever-increasing use of iodinated contrast media with percutaneous coronary intervention (PCI) in patients with poor renal function [1,2]. In western countries, CIN accounts for approximately 10% of all hospital-acquired renal failure [2–5], and the incidence rate increases markedly to as high as 44% among patients with pre-existing moderate renal failure [2,6]. Consequently, CIN is now the most important and critical complication after coronary angiography, and has led us to reconsider the effect of cardioprotective agents on the kidney. Risk factors for CIN reportedly include chronic kidney disease, diabetes mellitus, advanced age, congestive heart failure, nephrotoxic drug use, hypovolemia and excessive contrast medium volume [1,7]. Although the exact mechanisms underlying CIN remain unclear, current best practice calls for intravenous periprocedural volume expansion in at-risk patients, since no pharmacological approach has yet been shown to offer consistent protection.

Nicorandil (2-nicotinamidoethyl-nitrate ester) is a hybrid compound derived from an adenosine triphosphate (ATP)-sensitive potassium (K) channel (K-ATP channel) opener and a nitric oxide donor [8], and has been found to exert vasodilatory effects on the coronary vasculature, particularly small vessels, thereby increasing coronary blood flow [8]. It is therefore widely used to treat angina pectoris and acute heart failure in Japan and other Asian countries, as well as in Europe [8]. Nicorandil has been also exerted a pharmacologic cardiac preconditioning effect that improves microvascular circulation.

The kidney is a vascular organ that in some respects is similar to the heart. Moreover, K-ATP channel activity was recently reported to ameliorate renal ischemia-reperfusion injury in a rat model by preventing formation of reactive oxygen species (ROS) [9]. We therefore hypothesized that in patients who have poor renal function and who receive iodinated contrast media during PCI, nicorandil can be renoprotective, acting via mechanisms similar to those that underlie its cardioprotective effects.

To assess the protective effect of nicorandil against CIN in patients with poor renal function undergoing PCI, we conducted a prospective

* Corresponding author at: Department of Cardiology, Respirology, and Nephrology, Gifu University Graduate School of Medicine, Yanagido 1-1, Gifu City, Gifu 501-1194, Japan.
E-mail address: nissy@gifu-u.ac.jp (K. Nishigaki).

http://dx.doi.org/10.1016/j.ijcard.2015.05.078
0167-5273/

randomized trial comparing a group receiving intravenous hydration with saline plus continuous infusion of nicorandil with a control group receiving only the conventional saline hydration.

2. Methods

2.1. Study population

This study was done with written consent obtained from all patients prior to their enrollment in the study and after informing them of the content, importance and risks of the study, and in the absence of privacy intrusion. It was conducted in accordance with the principles of the revised Declaration of Helsinki and in accordance with good practice guidelines, and was approved by the local ethics committee on human research (Gifu University). Whenever a patient expressed a desire to discontinue registration, the registration was deleted. This study is registered at http://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi (study identifier: UMIN000008544, Nicorandil-CKD study).

Recently, the evaluation of cystatin C level for decreased renal function has been commonly used in not only Japan, but the western countries including the United States [10]. Cystatin C is one of the serum proteins and is the polypeptide of 120 amino acid residues belonging to the type 2 of the cystatin superfamily. It is produced with systemic nucleated cells and, as cysteine protease inhibitor, works in vivo. Cystatin C in blood is filtered with glomerule and is reabsorbed with proximal tubules. Cystatin C does not have such a character which affected by the muscle mass and gender like serum creatinine level. Therefore, cystatin C is superior to creatinine as a marker of the glomerular filtration rates (GFRs).

Therefore, we enrolled coronary artery disease (CAD) patients who would subsequently undergo elective PCI and who had a high cystatin C level, which was defined as a level greater than 0.95 mg/L in males and 0.87 mg/dL in females [11]. The indications for the procedure were determined by each patient's cardiologist. Exclusion criteria were end-stage renal failure on dialysis, a single functioning kidney, a history of kidney transplantation, hypotension with systolic blood pressures below 100 mmHg, acute myocardial infarction, acute heart failure, left ventricular ejection fraction (LVEF) less than 30% on echocardiogram or evidenced by pulmonary edema, multiple myeloma, pregnancy, a history of allergies to contrast medium or nicorandil, having received contrast medium within 7 days of study entry, having received an infusion of nicorandil within 1 month of study entry, parenteral use of diuretics, and the administration of N-acetylcysteine, metformin, sodium bicarbonate, teophiline, fenoldopam, mannitol, or a PDE-V inhibitor during the study.

2.2. Study protocol

This single-center (Gifu University Hospital), randomized controlled trial compared intravenous hydration plus continuous intravenous infusion of nicorandil with hydration alone as a means of preventing CIN in patients with poor renal function undergoing PCI.

Patients were randomly assigned to receive either nicorandil (Sigmart®, Chugai Pharma Co., Ltd., Tokyo, Japan; 2 vials of nicorandil (48 mg/V) dissolve in 100 mL 0.9% saline, and dripped it at speed of 0.1 mL/kg/h) plus 0.9% saline hydration intravenously infused at 1.0 mL/kg/h (nicorandil group) or 0.9% saline infusion only at 1.1 mL/kg/h (saline group). We used a random number which a member of Clinical Research Center of Gifu University Hospital generated in Microsoft Office Excel 2007® spread-worksheet (formula: = INT(101 + 898 * RAND())): an odd number indicates saline group, and an even number nicorandil group. The infusions were initiated 4 h prior to elective PCI and were continued for 24 h after the procedure (Fig. 1). All patients were encouraged to drink as soon as possible if they were thirsty. Iomeprol (Iomeron 350, Eisai Co., Ltd., Tokyo, Japan) or Iohexol (Omnipaque 350, Daiichi-Sankyo Co., Ltd., Tokyo, Japan), two nonionic, low-osmolality contrast media, were used in all patients. All decisions regarding procedural hemodynamics, including contrast volume, were left to the discretion of the cardiologist.

Serum creatinine and cystatin C were measured 4 h before PCI and 24 h, 48 h and 1 month after the procedure. The glomerular filtration rate (GFR) was calculated using the level-modified Modification of Diet in Renal Disease modified for Japanese patients: estimated GFR (eGFR) = $0.741 \times 175 \times \text{age in years}^{-0.203} \times \text{serum creatinine}^{-1.154}$; with female sex adjustment: eGFR female = eGFR × 0.742 [10].

Clinical outcome was adjudicated by an independent outside committee whose members were unaware of the treatment assignment. The primary end point was incident of CIN, defined as a 25% increase in serum creatinine or an increase in creatinine of 0.5 mg/dL from baseline at 48 h and at its maximum obtained within 1 month after the PCI. The secondary endpoints were percent rise in serum creatinine and cystatin C, percent decline in eGFR within 1 month after the procedure.

Serum cystatin C levels were measured based on the method of the sol particle homogenous immunoassay devised by Tanaka M. et al. (SRL, Tokyo, Japan) [12]. In summary, an aliquot of a sample (0.003 mL) was transferred by pipette to a cuvette, followed by 0.24 mL of reaction buffer. After 5 min at 37 °C, 0.06 mL of a solution of colloidal gold particles coated with anti-cystatin C antibodies was added and mixed. The reaction between the particles and any cystatin C in the sample results in the formation of agglutinates and a concomitant change in the absorbance signal, and the magnitude of the change in the absorbance signal

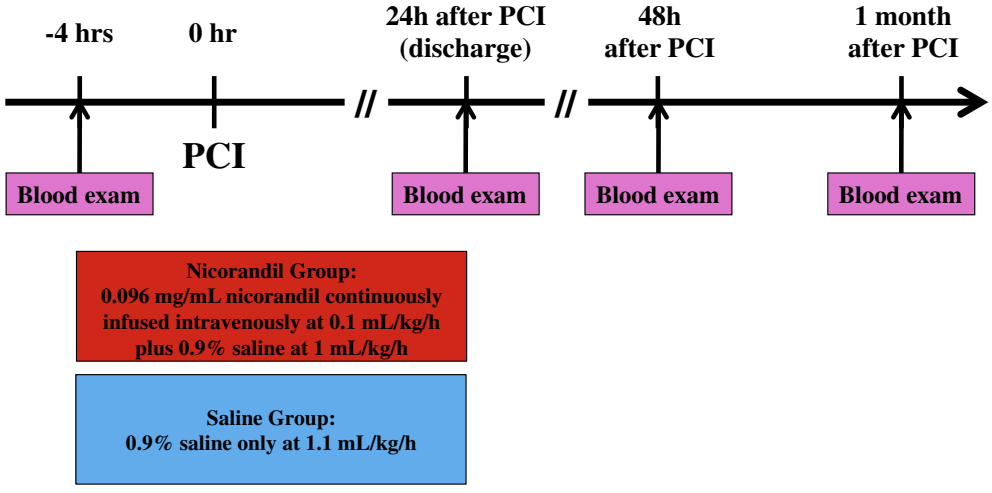

Fig. 1. Timeline used for the study participants. hrs: hours, PCI: percutaneous coronary intervention, Blood exam: blood examination.