Research Article

Efficacy of Oral Nicorandil to Prevent Contrast-Induced Nephropathy in Patients with Chronic Renal Dysfunction Undergoing an Elective Coronary Procedure

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Keywords

Nicorandil · Contrast-induced nephropathy · Chronic renal dysfunction

Abstract

Objectives: This prospective, randomized study was to investigate the role of nicorandil in the prevention of contrast-induced nephropathy (CIN) in patients with chronic renal dysfunction undergoing an elective coronary procedure. **Methods:** A total of 252 eligible patients were enrolled in this study and allocated into the control group ($n = 125$) or nicorandil group ($n = 127$). Both groups received the standard hydration treatment, and patients in the nicorandil group were orally administrated 10 mg of nicorandil (t.i.d.) beginning 2 days before and continuing for 2 days after an elective coronary procedure. Serum creatinine (SCr) and cystatin C (CysC) were measured at 24 h before and 24, 48, and 72 h after the procedure. The occurrences of CIN and adverse events within 1 year were recorded. **Results:** The nicorandil group had relatively lower SCr and CysC levels and a higher eGFR at 24 and 48 h after the procedure than the control group ($p < 0.05$). The incidence of CIN was significantly decreased in the nicorandil group compared to the control group. The multivariate logistic regression model revealed that nicorandil treatment was an independent protective factor for CIN (OR 0.669, 95% CI 0.522–0.857, $p = 0.001$). The multivariate COX proportional hazard model showed that nicorandil treatment was an independent protective predictor for adverse events (HR 0.881, 95% CI 0.781–0.993, $p = 0.037$). **Conclusions:** Nicorandil could exhibit a protective effect against CIN in patients with chronic renal dysfunction undergoing an elective coronary procedure and reduce the adverse events within 1 year after the procedure, which is superior to hydration treatment only.

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Introduction

Contrast-induced nephropathy (CIN), a form of acute kidney injury, is a serious complication that occurs after exposure to the iodinated contrast media [1–3]. With the ever-increasing use of iodinated contrast media with coronary interventional procedures, the incidence of CIN is increasing, especially in patients with poor renal function [4–6]. Recent studies have recognized that CIN is associated with long-term adverse events and mortality [7, 8]. Several approaches, such as hydration, N-acetylcysteine, sodium bicarbonate, and statins, have been studied to prevent CIN, but their therapeutic effects still need further investigation [9].

Nicorandil (2-nicotinamidoethyl-nitrate ester) is a hybrid compound derived from an adenosine triphosphate-sensitive potassium channel (K-ATP channel) opener and a nitric oxide donor, and has been widely used in the treatment of angina pectoris and acute heart failure [10, 11]. Nicorandil exhibits a vasodilatory effect on the coronary vasculature and a pharmacologic preconditioning effect to protect the heart from ischemia [10, 12]. Moreover, nicorandil could ameliorate ischemia-reperfusion injury in the rat kidney due to its ischemic preconditioning and anti-oxidant properties [13, 14]. Several studies have investigated the potential role of nicorandil in CIN prevention, but the results remain inconsistent. To the best of our knowledge, there has been no previous study with a long-term follow-up to evaluate the nephroprotective effect of nicorandil against CIN. This randomized, prospective trial was to assess the short-term and long-term protective effect of nicorandil against CIN and associated adverse events in patients with chronic renal dysfunction undergoing an elective coronary procedure.

Materials and Methods

Study Population

A total of 278 consecutive patients with renal dysfunction scheduled for coronary angiography or percutaneous coronary intervention (PCI) at our institution from January 2016 to January 2018 were considered for participation in our study. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m² calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Exclusion criteria were the following: end-stage renal disease; a history of kidney transplantation; left ventricular ejection fraction (LVEF) $< 35\%$ or New York Heart Association (NYHA) IV class; acute myocardial infarction; previous contrast media exposure within 1 week; allergy to contrast medium or nicorandil, and the administration of other medications, such as N-acetylcysteine, metformin, and sodium bicarbonate to prevent CIN. End-stage renal disease was defined as eGFR < 15 mL/min/1.73 m² or the need for long-term dialysis or kidney transplantation. LVEF was measured by echocardiography and calculated from the end-diastolic and end-systolic volumes calculated using the Simpson method from two orthogonal apical views.

Study Protocol

The study was a prospective, open-labeled, randomized controlled trial. Eligible patients were randomly allocated into either control or nicorandil groups, using a balanced block randomization method. Patients in the nicorandil group received 10 mg of nicorandil three times per day (t.i.d.), from 2 days before to 2 days after an elective coronary procedure. An elective coronary procedure was performed according to the standard technique by a radial or femoral approach. All enrolled patients received standard hydration with an intravenous

infusion of 0.9% saline at a rate of 1 mL/kg/h for 6 h before and 12 h after an elective coronary procedure. The nonionic contrast agent (Iopamidol injection, BRACCO Sine Ltd., China) was used for all patients.

Blood samples were collected at 24 h before and 24, 48, and 72 h after the procedure. Serum creatinine (SCr) was measured by an enzymatic method (Creatinine Diagnosis Kit, Roche Diagnostics, Germany), and Cystatin C (CysC) was determined by the immune turbidimetric method (Cystatin C Determination Kit, Mike Biotechnology Co. Ltd, China). CIN was defined as an SCr increase of $\geq 25\%$ and/or ≥ 0.5 mg/day within 72 h after exposure to the contrast medium.

Follow-Up

The median follow-up period of the study was 12.8 months. The follow-up endpoints were adverse events, including all-cause mortality, stroke, non-fatal myocardial infarction, percutaneous coronary revascularization, coronary artery bypass graft surgery, congestive heart failure, pulmonary edema, and end-stage renal disease. If more than one adverse event occurred in the same patient, the first event was used for the analysis. The follow-up data were obtained from electronic medical records and/or telephone interview with the patients or patients' caregivers. During the follow-up period, all the patients continued their regular medications without interruption.

Statistical Analysis

The incidence of CIN in the control group was approximate at 20%, while the incidence of CIN in the nicorandil group was hypothesized to be 5% according to the previous studies [15, 16]. The sample size was determined based on a two-sample, two-sided inequality test. The required number of participants was 93 per group, with the power of the test set at 90% and the significance level at 0.05. Taking into account the patients lost to follow-up (estimated at 20%), the number of patients enrolled in this study was at least 112 per group.

The continuous data are expressed as the mean $\pm$ standard deviation (SD) or median (interquartile range). The Kolmogorov-Smirnov test was used to analyze the normal distribution of continuous data. The Student *t* test, Mann-Whitney U test, or Wilcoxon rank-sum test was used for the comparisons of continuous variables. The categorical data were compared using χ^2 tests. Univariate and multivariate logistic regression analyses were used to identify the factors for CIN, while univariate and multivariate Cox proportional hazard analyses were carried out to determine the independent predictors for adverse events during 1 year of follow-up. Covariates with a *p* value < 0.10 after univariate analysis were entered into multivariate regression models. The cumulative adverse event rates were estimated by the Kaplan-Meier analysis and statistical differences were carried out using the log-rank test. The statistical significance was considered as a 2-tailed *p* < 0.05 . Statistical analyses were performed using SPSS version 22.0.

Results

Of the 278 patients enrolled in this study, 8 (2.88%) were excluded because of incomplete medical data, and another 5 (1.80%) were withdrawn from the study at their own request. A total of 265 patients (95.32%) were randomized to either receive nicorandil and hydration (nicorandil group, *n* = 133) or hydration only (control group, *n* = 132). During the 1-year follow-up period, 6 patients from the nicorandil group and 7 patients from the control group missed the follow-up. Consequently, 127 patients in the nicorandil group and 125 patients in the control group completed the study. The study flowchart is depicted in Figure 1.

Fig. 1. Study flowchart.

Patients' Baseline Characteristics

The baseline clinical characteristics of the patients are summarized in Table 1 and the angiographic and procedural characteristics are presented in Table 2. No significant differences were observed between the two groups in age, gender, underlying diseases, laboratory results, medications, and angiographic/procedural features.

Changes in Indicators of Renal Function

As the enrolled patients had poor renal functions, both groups had relatively high basal SCr and CysC, and low eGFR. Additionally, there was no significant difference in the volume of contrast medium used between the nicorandil group (128.3 ± 37.2 mL) and the control group (122.8 ± 35.9 mL; $p = 0.234$).

Baseline and post-procedural levels of SCr, eGFR, and CysC are compared between the two groups in Table 3. The levels of SCr and CysC of both groups were increased at 24 and 48 h after an elective coronary procedure, whereas no significant differences were found at 72 h after procedure, compared to the baseline levels. The levels of SCr and CysC peaked at 48 and 24 h, respectively. eGFR levels of both groups declined at 24 and 48 h, and then increased to baseline levels at 72 h. The levels of SCr and CysC at 24 and 48 h were lower, whereas the levels of eGFR at 24 and 48 h were higher in the nicorandil group compared with those of the control group.

Table 1. Patients' baseline clinical characteristics

	Nicorandil group (n = 127)	Control group (n = 125)	p value
Age, years	62.25±16.63	65.87±17.62	0.095
Male	76 (59.84)	67 (53.60)	0.317
BMI	24.35±5.87	23.78±5.98	0.446
Smoking	31 (24.41)	27 (21.6)	0.596
Hypertension	68 (53.54)	62 (49.6)	0.531
Diabetes	81 (63.78)	75 (60)	0.537
Laboratory results			
Hemoglobin, g/L	127.52±21.52	131.56±23.37	0.155
Total cholesterol, mmol/L	4.46±1.21	4.37±1.19	0.552
LDL-C, mmol/L	2.74±0.79	2.71±0.81	0.766
hsCRP, mg/dL	7.16±3.42	7.41±3.25	0.553
BNP, µg/L	72.71±17.28	75.63±18.33	0.194
LVEF, %	51.39±10.35	53.58±12.77	0.136
Medications			
Aspirin	108 (85.04)	101 (80.80)	0.371
Clopidogrel	83 (65.35)	79 (63.20)	0.721
ACEI/ARB	46 (36.22)	44 (35.20)	0.866
Calcium-channel blocker	50 (39.37)	56 (44.80)	0.383
β-Blockers	61 (48.03)	53 (42.40)	0.369
Statins	89 (70.08)	83 (66.40)	0.530

Data are presented as the mean ± SD or n (%). BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

Table 2. Procedural variables

	Nicorandil group (n = 127)	Control group (n = 125)	p value
Hospital days	6.85±1.33	7.18±1.65	0.081
PCI	74 (58.27)	82 (65.60)	0.231
Target lesion			0.713
LAD	72 (56.69)	65 (52.00)	
LCX	32 (25.20)	33 (26.40)	
RCA	23 (18.11)	27 (21.60)	
Stents per patient, n	1.63±0.91	1.72±0.86	0.421
Surgery time, min	51.37±10.38	53.41±11.25	0.136
Contrast medium volume, mL	128.39±37.25	122.81±35.92	0.227

Data are presented as the mean ± SD or n (%). PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Incidence of CIN

Overall, CIN was diagnosed in 27 (10.71 %) of the 252 patients within 72 h after an elective coronary procedure, which consisted of 8 patients in the nicorandil group and 19 patients in the control group. The incidence of CIN was lower in the nicorandil group than the control group (6.30 vs. 15.20%, $p = 0.022$; Fig. 2).

Table 3. Comparisons of markers of renal function between the two groups

	Nicorandil group (n = 127)	Control group (n = 125)	p value
SCr, $\mu\text{mol/L}$			
Baseline	121.22 $\pm$ 22.35	118.75 $\pm$ 26.18	0.421
24 h	124.35 $\pm$ 26.45	131.36 $\pm$ 27.89	0.042
48 h	129.87 $\pm$ 25.78	137.19 $\pm$ 30.18	0.039
72 h	118.74 $\pm$ 23.69	123.16 $\pm$ 27.37	0.171
eGFR, mL/min/1.73 m^2			
Baseline	59.32 $\pm$ 19.31	61.75 $\pm$ 22.56	0.359
24 h	56.73 $\pm$ 15.64	52.66 $\pm$ 14.82	0.035
48 h	49.35 $\pm$ 13.98	45.7 $\pm$ 12.61	0.031
72 h	58.29 $\pm$ 17.64	57.31 $\pm$ 18.77	0.670
CysC, mg/L			
Baseline	1.17 $\pm$ 0.28	1.12 $\pm$ 0.29	0.165
24 h	1.38 $\pm$ 0.44	1.52 $\pm$ 0.58	0.032
48 h	1.36 $\pm$ 0.51	1.49 $\pm$ 0.38	0.023
72 h	1.19 $\pm$ 0.34	1.2 $\pm$ 0.37	0.823

Data are presented as the mean $\pm$ SD. SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CysC, cystatin C.

Fig. 2. Incidence of CIN. The nicorandil group had a higher CIN incidence than the control group.

Independent Predictors for the Development of CIN

Univariate analysis results revealed that age, diabetes, contrast volume, and nicorandil treatment were associated with CIN. In the multivariate logistic regression analysis (Table 4), nicorandil treatment was found to be an independent protective factor for CIN (OR 0.669, 95% CI 0.522–0.857, $p = 0.001$), while diabetes was also an independent risk factor for CIN (OR 1.429, 95% CI 1.065–1.918, $p = 0.017$).

Adverse Events during the 1-Year Follow-Up

During the follow-up period, of the 252 patients, 60 (24 in the nicorandil group and 36 in the control group) experienced adverse events. The adverse events of the two groups are summarized in Table 5. Overall, the nicorandil group had fewer adverse events (18.1 vs.

Table 4. Multivariate logistic regression analysis for the independent predictors of CIN

Variable	β	Wald	OR	95% CI	<i>p</i> value
Age	0.362	2.368	1.436	0.906–2.277	0.124
Diabetes	0.357	5.647	1.429	1.065–1.918	0.017
Nicorandil	–0.402	10.163	0.669	0.522–0.857	0.001
Contrast volume	0.571	1.589	1.770	0.728–4.301	0.207

Table 5. Distribution of adverse events in the two groups

	Nicorandil group (<i>n</i> = 127)	Control group (<i>n</i> = 125)
Nonfatal MI	3 (2.36)	5 (4.00)
Revascularization	6 (4.72)	10 (8.00)
Ischemic stroke	4 (3.15)	6 (4.80)
Coronary artery bypass graft surgery	1 (0.79)	2 (1.60)
Congestive heart failure	5 (3.94)	5 (4.00)
Pulmonary edema	2 (1.57)	2 (1.60)
End-stage kidney disease	2 (1.57)	4 (3.20)
Cardiac death	1 (0.79)	2 (1.60)

Fig. 3. Kaplan-Meier curve of the cumulative incidence of adverse events during the follow-up period.

28.8%, $p = 0.032$) than the control group. Kaplan-Meier curve analysis revealed that the cumulative adverse event rate was significantly lower in the nicorandil group compared to the control group (log-rank: 4.834, $p = 0.028$; Fig. 3). Meanwhile, Spearman's correlation analysis revealed that the CIN occurrence was positively correlated with adverse events ($r = 0.415$, $p < 0.001$).

Table 6. Multivariate Cox proportional hazards analysis for adverse events

	β	Wald	HR	95% CI	<i>p</i> value
Age	0.162	5.098	1.176	1.022–1.353	0.024
Hypertension	0.372	2.524	1.451	0.917–2.295	0.112
Diabetes	0.118	4.118	1.125	1.004–1.261	0.042
Nicorandil	−0.127	4.329	0.881	0.781–0.993	0.037

Independent Predictors for Adverse Events

In the univariate Cox proportional hazard analysis, age, hypertension, diabetes, and nicorandil treatment were found to be significantly associated with adverse events. After adjusting for covariates, age (HR 1.176, 95% CI 1.022–1.353, $p = 0.024$), diabetes (HR 1.125, 95% CI 1.004–1.261, $p = 0.042$), and nicorandil treatment (HR 0.881, 95% CI 0.781–0.993, $p = 0.037$) remained significant predictors for adverse events in the multivariate Cox regression (Table 6).

Discussion

The present study evaluated nicorandil treatment in patients with chronic renal dysfunction undergoing an elective coronary procedure to determine whether the treatment could prevent CIN. The major findings of our study were that nicorandil could reduce the incidence of CIN and also decrease the occurrence of adverse events over 1 year of follow-up.

The exact pathophysiology of CIN remains unclear. Several mechanisms may contribute to the pathogenesis of CIN, including the direct cytotoxic effects of contrast media on renal epithelial cells because of its high osmolality, activated tubuloglomerular feedback, impaired production of nitric oxide, adenosine, endothelin, prostaglandin, and angiotensin resulting in imbalance between renal vasodilation and vasoconstriction, and increased renal interstitial pressure, which were all attributed to the hypoxia of the medulla and acute tubular necrosis [17–20]. Regarding possible mechanisms, many preventive measures have been investigated for protection against CIN. Hydration, N-acetylcysteine, sodium bicarbonate, statins, and acetylcysteine were all studied, but many of them still remain controversial [21–23].

Nicorandil, a nicotinamide derivative, is widely used in the treatment of angina and heart failure. Nicorandil exerted cardioprotective properties by preventing reperfusion injury via promoting ischemic preconditioning, protecting against myocardial ischemia through its vasodilatory effects as a nitric oxide donor, and improving microvascular circulation [10–12]. Large-scale population-based studies, such as the Impact of Nicorandil in Angina (IONA) study [24] and Japanese Coronary Artery Disease (JCAD) study [25], confirmed that nicorandil could significantly reduce the incidence of major adverse cardiovascular events in patients with coronary heart diseases. Additionally, several basic studies demonstrated the nephroprotective potential of nicorandil. Zhang et al. [14] reported that pretreatment with nicorandil could protect against renal ischaemia-reperfusion injury by inhibiting the production of inflammatory cytokines and restoring the expression of KIR6.2 in a rat model. Also, Tamura et al. [26] found that nicorandil could reduce albuminuria and alleviate chronic renal injury through blocking oxidative stress.

Several studies have investigated the potential role of nicorandil in CIN prevention, but the results are inconsistent. Nawa et al. [27] reported that nicorandil continuously infused

intravenously at 1 mL/kg/h beginning at 4 h before the procedure and continuing for 24 h after it could have a favorable nephroprotective effect against CIN in patients with poor renal function. Fan et al. [16] found that orally administrated nicorandil (10 mg, t.i.d.) could prevent CIN in patients with renal insufficiency. Zhang et al. [28] reported that prophylactic administration of nicorandil could prevent CIN in patients with moderate renal insufficiency undergoing PCI. Meta-analyses conducted by both Li et al. [29] and Wang et al. [30] confirmed that nicorandil can reduce the incidence of CIN in patients exposed to contrast medium. However, another recent study undertaken by Ko et al. [31] reported that prophylactic intravenous infusion of 12 mg of nicorandil prior to the coronary angiography could not decrease the incidence of CIN in patients with renal dysfunction undergoing coronary angiography. The exact reason for the discrepancy between these studies was unclear, which might be due to the differences in the administration schedule of nicorandil. The mean elimination half-life of nicorandil is very short, reported to be 0.8–1.3 h in both normal volunteers and patients with impaired renal function [32], while the elimination half-life of contrast medium is relatively long (approx. 2 h in healthy individuals and 4 h in patients with mild renal disease) [33]. Therefore, the administration of nicorandil after the procedure was very critical to prevent against CIN. In our study, the patients received oral nicorandil (10 mg t.i.d.) beginning 2 days before and continuing for 2 days after the procedure. Our results showed that continuous nicorandil treatment could significantly reduce the incidence of CIN, which is in accordance with the studies by Nawa et al. [27] and Fan et al. [16].

Recently, increasing attention has been paid to the relationship between CIN and long-term clinical outcomes in patients undergoing an elective coronary procedure. CIN may lead to end-stage renal disease and major adverse cardiovascular events [34]. Abe et al. [35] found that CIN was associated with increased mortality in patients who underwent PCI with chronic kidney diseases. Solomon et al. [3] demonstrated that CIN was associated with increased long-term adverse events, including revascularization, coronary artery bypass graft surgery, myocardial infarction, and mortality, in renally impaired patients undergoing coronary angiography. In our study, CIN showed a significant positive correlation with adverse events in 1 year, which was consistent with previous studies. Additionally, the incidence of adverse events was decreased in the nicorandil group and nicorandil was found to be a protective predictor for the presence of adverse events, which was probably associated with the cardio-protective and renoprotective properties of nicorandil. Moreover, to the best of our knowledge, our study is the first to report 1-year follow-up outcomes of prophylactic administration of nicorandil in patients with chronic renal dysfunction undergoing an elective coronary procedure.

There were several limitations to this study. This was not a blinded study. A larger, multi-center and double-blinded study would be needed to confirm the effectiveness of nicorandil in preventing CIN in patients with chronic renal dysfunction. Most of the subjects recruited into this study had mild-stage renal dysfunction, meaning we cannot conclude the nephro-protective effect of nicorandil against CIN in patients with severe renal dysfunction.

In conclusion, this study suggests that nicorandil has a nephroprotective effect against CIN in patients with chronic renal dysfunction undergoing an elective coronary procedure. Additionally, nicorandil could be helpful to decrease the incidence of adverse events after the procedure.

Statement of Ethics

Subjects have given their written informed consent. The study protocol was approved by the Ethics Committee of the Civil Aviation General Hospital.

Disclosure Statement

The authors declare that they have no competing interests.

Author Contributions

Z.F. was principally responsible for the conception and design of the study, and prepared the first draft of the manuscript. Y.L., H.J., and X.J. contributed to the data acquisition and performed the statistical analyses. Y.L. revised the manuscript. All authors read and approved the final manuscript prior to submission.

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