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Comparison of double-dose vs. usual dose of nicorandil for the prevention of contrast-induced nephropathy after cardiac catheterization

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Abstract

Purpose Contrast-associated nephropathy (CIN), the third main reason of the acute kidney injury (AKI) in inpatients, is a potentially severe side effect of angiography and the preventive role of nicorandil on CIN is still controversal. The aim of this clinical trial was to evaluate the preventive role of different doses of nicorandil on CIN in patients experiencing cardiac catheterization compared with hydration.

Methods We recorded outcomes from 330 patients who were randomly divided to either a double-dose (30 mg/day) nicorandil group or to a usual-dose (15 mg/day) nicorandil group or a control group (hydration only). The primary endpoint of the current research was the occurrence of CIN, which is defined as a relative elevation of SCr level of 25% above the baseline or an absolute increment of SCr of more than 44.2 μmol/L (0.5 mg/dL) within 48 or 72 h after contrast medium exposure. Additional endpoints were the changes in BUN, SCr, Cys-C, eGFR, and CRP level within 48 h after contrast agent exposure and major adverse events occurring during hospitalization and 14 days of follow-up.

Results 6 out of 111 patients (5.4%) had contrast-induced nephropathy in the double-dose group and it occured 11 out of 107 patients (10.3%) in the usual-dose group, 16 out of 112 patients (14.3%) in the control group. There was a significant difference in the occurrence of CIN between the double-dose group and the control group at 48 h after taking the radiocontrast medium ($p = 0.026$) while no such significant difference observed in the usual-dose group and the control group ($p = 0.367$), the double-dose group and usual-dose group ($p = 0.180$) as well.

Conclusions Daily peri-procedural usual-dose nicorandil could just relieve contrast-induced renal injury, only double-dose nicorandil was associated with a reduced incidence of CI-AKI compared with hydration.

Keywords Contrast-induced nephropathy · Nicorandil · Percutaneous coronary intervention · Prevention

Introduction

Contrast-induced nephropathy (CIN), defined as > 44.2 μmol/L (0.5 mg/dL) rise or > 25% elevation in serum creatinine concentration within 48 h after percutaneous coronary intervention (PCI) compared with pre-PCI without an alternative cause [1], is a prevalent and serious complication which elicited by radiologic procedures using intravascular iodinated contrast media injection. The exact pathological mechanisms contributing to CIN are complex and still controversial. Risk factors for CIN development are as follows: diabetes mellitus, congestive heart failure (CHF), advanced age, hypertension, hypotension, declined renal perfusion, female gender, high-osmolar contrast, hypovolemia, excessive radiocontrast agent volume, urgent or planned PCI and most importantly, chronic kidney disease (CKD) [2]. The odds of CIN are rising, ranging from about 2% in low-risk patients subset to 50% in selected populations. CIN is the third major cause of acute kidney injury (AKI), leading to an increment in healthcare costs, hospital stay, and mortality [3]. Many pharmacologic and therapeutic strategies have been applied to decline the occurrence of CIN, such as hydration, statin, sodium bicarbonate, fenoldopam, natriuretic peptide, *N*-acetylcysteine, vitamins,

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theophylline, prostaglandin, ascorbic acid, and other agents [4]. At present, peri-procedural administration of hydration, using iso and/or low osmolar contrast agents minimizing the volume of contrast media, is the confirmed approach against CIN [5, 6].

Nicorandil is a K-ATP channel opener containing a nitric oxide donor with the property of vasodilatory effect on the coronary vasculature, thereby increasing coronary blood perfusion [7]. Therefore, it is widely applied as anti-angina medication in clinical practice. Animal studies presented that K-ATP channel openers, such as nicorandil, could ameliorate renal injury caused by ischemia–reperfusion injury [8, 9]. The efficacy of nicorandil for the prevention of CIN remains controversal. It is hypothesized that the preventive effect of nicorandil on CIN depends on its dose. Accordingly, the current study is sought to compare different doses (double-dose vs. usual-dose) of nicorandil in preventing contrast-induced acute kidney injury in a prospective, randomized trial in patients undergoing planned PCI.

Methods

Study population

Our study reviewed all consecutive patients who underwent non-emergent PCI or coronary angiography (CAG) at Tianjin Chest Hospital between June 2017 and December 2018. The exclusion criteria were as follows: pregnancy, lactation, used contrast agents within 1 week before PCI, allergy to contrast dye or use of low-permeability contrast agent, cardiovascular surgery or end-stage renal disease {creatinine clearance (Ccr) < 15 mL/min; Ccr = [140 − age] × weight (kg)/[0.818 × Scr (μmol/L)](× 0.85 if female)} or renal replacement, malignant neoplasms, balloon counterpulsation treatment (IABP); thyroid dysfunction, coagulopathy.

Study protocol

Based on these criteria, a total of 330 Eligible patients were randomly divided into the double-dose group ($n = 111$, 30 mg/day) or the usual-dose group ($n = 107$, 15 mg/day) or control group ($n = 112$, hydration only) by random numbers generated by a computer, using undisclosed code and recorded by a nurse. We compared the in-hospital outcomes between the intervention group (double-dose/usual-dose group) and control group, respectively, and divided them into two subgroups. Patients in the double-dose group received nicorandil of about 10 mg diluted in 100 mL of 0.9% saline three times daily (beginning 2 days prior to the coronary intervention and continuing 2 days after it), plus 0.9% saline (at speed of 1.0 mL/kg/h, 0.5 mL/kg/h for patients with LVEF < 40%) intravenously administered from 12 h before to 12 h following the intervention. Nicorandil of 5 mg and the same volume of hydration were given to the patients in the usual-dose group by the same method. The control group only received hydration treatment (same volume of 0.9% saline). Both the clinicians and patients were fully blinded to group outcomes and treatment interventions. Because hydration is recognized as the golden-standard prophylactic measure in preventing CIN, all recruited patients were encouraged to drink as much as water if they were thirsty. Drug delivery and hydration were conducted by the nurses. In-hospital events were carefully monitored and recorded by well-trained nurses. Aspirin, clopidogrel, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, beta receptor antagonists, statins, and diuretics were used according to the interventional cardiologist's discretion and based on clinical requirements or recommendations in guidelines. All patients were treated with non-ionic, low-osmolar iodinated contrast medium during the procedure. Blood samples were collected at hospital admission and on days 1 and 2 after the procedure for the measurement of the levels of blood urea nitrogen (BUN), Scr, cystatin-C (Cys-C), GFR, and C-reactive protein (CRP).

Study endpoints

The primary endpoint of the research was the development of CIN, defined as > 44.2 μmol/L (0.5 mg/dL) rise or > 25% elevation in serum creatinine concentration within 48 h after PCI compared with pre-PC. Additional endpoints were the changes in BUN, Cys-C, SCr, eGFR, and CRP within 48 h after contrast agent exposure and major adverse events (including all-cause mortality, renal replacement therapy, stroke, acute heart failure, and pulmonary edema) occurring during hospitalization and 14-day follow-up period.

Statistical analysis

Unpaired Student's *t* test was done to compare normally distributed continuous variables (described as mean ± standard deviation). Non-normally distributed continuous variables (expressed as median and interquartile range) were analyzed via the non-parametric rank-sum test, as appropriate. Comparisons of categorical data, expressed as a number (percentages) were tested by Chi-squared or Fisher's exact tests when the expected frequency < 5. Investigators used multivariate logistic regression analysis as a mean of excluding the influence of confounding factors. Based on available research [4], the rate of CIN was approximated to 13% in the control group. Treatment with nicorandil was hypothesized to reduce this incidence to 5%. Accordingly, at least 65 patients from each group were needed based on a beta error level of 0.10 and an α error level of 0.05. Value of $p < 0.05$ was

considered significant (two sided). All statistical analyses were performed using IBM SPSS software.

Results

Baseline characteristics

Initially, 357 patients were suitable for the inclusion criteria totally, with 27 meeting exclusion criteria and being excluded. Finally, 111 patients in the double-dose group, 107 in the usual-dose group, and 112 in the control group remained for statistical analysis. Detailed characteristics of the 330 patients are presented in Table 1. No significant differences were observed between the two subgroups before PCI concerning baseline characteristics ($p > 0.05$).

Occurrence of CIN and multivariate logistic regression analysis

CIN was diagnosed in 6 (5.4%) patients in the double-dose group, 11 (10.3%) patients in the usual-dose group, and 16 (14.3%) in the control group; 30 (9.1%) patients developed CI-AKI in total. There was a significant difference in the prevalence between the double-dose group (30 mg/day) and the control group ($p = 0.026$), but this difference was not observed between the usual-dose group (15 mg/day) and control group ($p = 0.367$). Multivariate logistic regression analysis was conducted to identify factors related to the development of CIN, such as contrast volume, diuretics, diabetes, hydration volume, hypertension, age, and nicorandil (Table 2). Multivariate logistic regression results revealed that double-dose nicorandil was associated with a reduction of CIN compared to saline group, while usual-dose group was not.

Major adverse events during the in-hospital stay and 14-day follow-up period

Major adverse events occurred in two patients (one acute heart failure, one stroke) in the double-dose group and

Table 2 Multiple logistic regression analysis

Variables	OR	95% CI	*p* value
Contrast volume	1.002	0.994–1.010	0.649
Hydration amount	1.000	0.999–1.002	0.867
Hypertension	1.174	0.526–2.618	0.695
Diabetes	0.535	0.217–1.322	0.175
Diuretics	0.509	0.132–1.955	0.325
Group 1 (double-dose vs. hydration)	0.356	0.128–0.991	0.048
Group 2 (usual-dose vs. hydration)	0.480	0.185–1.246	0.132

Table 1 Comparison of baseline characteristics between the two subgroups

Variables	Double-dose group	Control group	*p* value	Usual-dose group	Control group	*p* value
Age (years)	65.37 ± 7.19	66.69 ± 7.33	0.177	67.09 ± 6.85	66.69 ± 7.33	0.673
Diabetes (%)	19 (17.1)	18 (16.1)	0.834	21 (19.6)	18 (16.1)	0.492
Male (%)	78 (70.2)	67 (39.8)	0.102	73 (68.2)	67 (39.8)	0.408
BMI (kg/m^2)	24.67 ± 3.10	24.60 ± 3.34	0.882	24.85 ± 2.63	24.60 ± 3.34	0.536
Hypertension	42 (37.8)	59 (52.7)	0.196	69 (64.5)	59 (52.7)	0.723
HDL (mmol/L)	1.40 ± 0.39	1.28 ± 0.34	0.013	1.35 ± 0.39	1.28 ± 0.34	0.179
LDL (mmol/L)	2.65 ± 0.76	2.72 ± 0.92	0.564	2.59 ± 0.92	2.72 ± 0.92	0.297
Hemoglobin (g/L)	132.83 ± 15.27	132.62 ± 17.40	0.925	134.27 ± 16.23	132.62 ± 17.40	0.472
Triglycerides (mmol/L)	1.75 ± 0.51	1.82 ± 0.54	0.317	1.76 ± 0.51	1.82 ± 0.54	0.454
Cholesterol (mmol/L)	4.63 ± 0.99	4.56 ± 0.92	0.567	4.59 ± 0.80	4.56 ± 0.92	0.761
Hydration amount (mL)	1181.52 ± 210.87	1201.28 ± 329.82	0.595	1172.77 ± 280.66	1201.28 ± 329.82	0.493
Aspirin (%)	111 (100)	112 (100)	1.000	107 (100)	112 (100)	1.000
Clopidogrel (%)	111 (100)	112 (100)	1.000	107 (100)	112 (100)	1.000
β-Antagonist (%)	81 (73.0)	93 (83.8)	0.07	80 (74.8)	93 (83.8)	0.133
ACEI/ARB (%)	56 (50.5)	46 (41.1)	0.160	56 (52.3)	46 (41.1)	0.052
Calcium antagonists (%)	13 (11.7)	19 (17.0)	0.263	15 (14.0)	19 (17.0)	0.547
Diuretics (%)	8 (7.20)	7 (6.30)	0.775	7 (6.50)	7 (6.30)	0.087
Contrast volume (mL)	180.29 ± 46.78	184.79 ± 53.05	0.503	172.83 ± 49.66	184.79 ± 53.05	0.087
LVEF < 45%	13 (11.7)	9 (8.0)	0.357	5 (4.7)	9 (8.0)	0.309

Data are expressed as mean ± SD or *n* (%)

BMI body mass index, *LVEF* left ventricular ejection fraction, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers

three patients (one ventricular fibrillation and one temporary dialysis) in the usual-dose group, five patients in the control group (four acute heart failures, one ventricular fibrillation) during hospitalization and the 14-day follow-up period. There were no significant differences between the nicorandil groups (double dose/usual-dose) and the control group ($p=0.254$, $p=0.513$, respectively) in the incidence of major adverse events.

Changes in BUN, Scr, Cys-C, CRP, and development of CIN

Changes in parameters of renal function, including BUN, Scr, Cys-C, CRP, and GFR were compared between the two subgroups, respectively (Table 3). There were no significant differences in BUN, Scr, CysC, CRP, and GFR at baseline between the intervention groups and the control group before PCI. In both the nicorandil groups and the control group at 48 h after the operation, BUN, SCr, Cys-C, CPR, and GFR were higher compared with baseline, with SCr in the double-dose group significantly lower than that in the control group ($p=0.018$), while just slight difference between the usual-dose group and the control group ($p=0.370$). in the nicorandil groups, it is significantly lower compared with the control group in post-procedure Cys-C and CRP levels ($p=0.000$). Nevertheless, GFR decreased dramatically following the operation in all three groups, patients in the double-dose group exhibited significantly higher in GFR than the saline group ($p=0.047$), while no significant difference between usual-dose group and the control group ($p=0.921$). Our date indicates that treatment with double-dose nicorandil was related to significantly less increment of SCr and less decline of GFR, while usual-dose nicorandil only decreased post-procedure Cys-C and CRP levels. Table 4 indicates the development of CIN. 6 out of 111 patients (5.4%) had contrast-induced nephropathy in the double-dose group and it occured 11 out of 107 patients (10.3%) in the usual-dose group and 16 out of 112 patients (14.3%) in the control group. There was a significant difference in the occurrence of CIN between the double-dose group and the control group at 48 h after taking the radiocontrast medium ($p=0.026$) while no such significant

Table 3 Biochemical data before and following coronary intervention

Variables	Double-dose group	Control group	*p* value	Usual-dose group	Control group	*p* value
BUN (mmol/L)						
Baseline	5.67 ± 1.39	5.74 ± 1.42	0.705	5.72 ± 1.64	5.74 ± 1.42	0.942
48 h post-procedure	5.92 ± 1.06	6.06 ± 1.08	0.339	6.03 ± 1.21	6.06 ± 1.08	0.859
Scr (μmol/L)						
Baseline	79.14 ± 18.20	76.62 ± 14.46	0.158	78.46 ± 9.95	76.62 ± 14.46	0.276
48 h post-procedure	83.09 ± 20.97	89.87 ± 22.71	0.018*	87.66 ± 11.64	89.87 ± 22.71	0.370
Cys-C (mg/L)						
Baseline	0.93 ± 0.22	0.95 ± 0.20	0.389	0.95 ± 0.25	0.95 ± 0.20	0.938
48 h post-procedure	1.24 ± 0.51	1.80 ± 0.41	0.000*	1.27 ± 0.38	1.80 ± 0.41	0.000*
CRP (mmol/L)						
Baseline	4.82 ± 1.44	4.93 ± 1.21	0.519	5.11 ± 1.35	4.93 ± 1.21	0.296
48 h post-procedure	10.49 ± 3.58	16.43 ± 4.13	0.000*	13.45 ± 3.29	16.43 ± 4.13	0.000*
Incidence of major adverse events, *n* (%)	2 (1.8%)	5 (4.5%)	0.254	3 (2.8%)	5 (4.5%)	0.513
GFR						
Baseline	80.20 ± 23.98	81.42 ± 26.84	0.719	77.41 ± 16.82	81.42 ± 26.84	0.188
48 h post-procedure	77.21 ± 21.90	70.97 ± 24.66	0.047*	70.69 ± 16.10	70.97 ± 24.66	0.921

BUN blood urea nitrogen, *Scr* serum creatinine, *Cys-C* cystatin-C, *CRP* C-reactive protein

*$p<0.05$ compared with baseline

Table 4 Odds of CIN

	Double-dose group	Control group	*p*	Usual-dose group	Control group	*p*	Double-dose group	Usual-dose group	*p*
Odds of CIN, *n* (%)	6 (5.4)	16 (14.3)	0.026*	11 (10.3)	16 (14.3)	0.367	6 (5.4)	11 (10.3)	0.180

*$p<0.05$

difference observed in the usual-dose group and the control group ($p = 0.367$), the double-dose group and usual-dose group ($p = 0.180$) as well.

Discussion

In the present study, association between peri-procedural doses of nicorandil (15 or 30 mg/day) and the incidence of CIN was evaluated. Our research revealed that the peri-procedural high dose might be related to a declined rate of CIN compared with control group, while the usual-dose dose not. The treatment of nicorandil presents a favorable therapy to decrease procedure-related contrast-induced nephropathy after percutaneous endovascular intervention. Nicorandil may present renoprotection via elevating blood flow to the renal microvasculature, the renal tubules in particular, through NO-mediated vasodilatation and suppression of ROS formation. Unexpectedly, the angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists (ACEI/ARB) use strengthened our conclusion. Based on previous researches, ACEI/ARB could increase the risk of CIN. In our study, use of ACEI/ARB was lower compared with the double-dose group or the usual-dose group, while the odds of CIN were significantly higher in the control group. The exact pathogenesis of CIN has not been fully determined. It is thought that contrast-mediated inflammatory responses and oxidative stress are the most important factors contributing to the pathogenesis of CIN [10]. Currently, nicorandil is widely used in the treatment of angina and acute heart failure [11]. K-ATP channels, broadly distributed in various tissues, are viewed as sensors of glucose and oxygen due to its ability of responding to change in the metabolic activity of the cell [12, 13]. Nicorandil has been found to exert a cardioprotective effect against ischemic–reperfusion injury [14]. A recent research suggested that activation of K-ATP channels alleviated renal injury induced by ischemia–reperfusion via minimization of the accumulation of reactive oxygen radicals (ROS) [9].

Shimizu et al. [9] found that, in the ischemia–reperfusion injury rat model, the level of the KIR6.2 channels (a major sub-unit of the KATP channel) was significantly lower than that in the control group. However, the pretreatment could reverse the down-regulation of the KIR6.2.

Takahide et al.'s research showed that double-dose nicorandil decreased the odds of CI-AKI compared to the control group, which is consistent with our conclusion. Furthermore, meta-analysis had also suggested that peri-procedural short-term intensive nicorandil treatment is likely effective in preventing CI-AKI. However, Young et al.'s analysis showed that prophylactic intravenous infusion of nicorandil did not decrease the incidence of CIN. In the study by Ko et al., a total of 81 patients with an eGFR 60 mL/min or less were treated with nicorandil, 12 mg in total, intravenously for 30 min prior to coronary procedure. This study revealed that prophylactic intravenous infusion of nicorandil did not decrease the risk of CIN in patients with renal insufficiency undergoing coronary angiography [15]. In another study by Fan et al., 120 patients with an eGFR < 60 mL/min who were experiencing planned cardiac catheterization received nicorandil of 10 mg orally, three times daily from 2 days before to 3 days after the procedure. In that study, the incidence of CIN at 48 h after procedure was significantly lower in nicorandil group compared to the control group [16]. This was in accordance with the present study that intravenously administered high-dose nicorandil decreases the incidence of CIN in patients undergoing elective cardiac catheterization.

Hydration is the gold-standard preventive measure in the prevention of CI-AKI [17]. However, there is no standardized protocol for oral or intravenous peri-procedural hydration, so we could not evaluate the preventative effect of oral hydration. Nevertheless, oral hydration may be as effective as intravenous rehydration for preventing CI-AKI [18, 19]. Thus, it is possible that the different hydration volumes between the groups might have influenced the observed benefit of double-dose nicorandil.

Conclusions

Taken together, our observational data suggest that daily peri-procedural double-dose nicorandil was associated with a reduced risk of CI-AKI compared with hydration only, while the usual-dose group did not, just improved renal function slightly. Nevertheless, further well-designed studies are warranted to confirm these conclusions.

Limitations of the study

The current study is subject to a series of limitations. First, this prospective observational study did not use randomization, and was conducted at a single centre, which may weaken the statistical power of our conclusions. Second, variations in the measurement times may have caused us to miss post-procedure peak of creatinine levels. Furthermore, around half of the patients were discharged at 2 days after CAG, so their serum creatinine concentrations could not be measured on day 2. Thus, this variation and lack of data may have led to an underestimation of the true CI-AKI incidence in the study population. Fourth, the time from nicorandil loading to contrast exposure varied in different patients. Furthermore, there is no standardized protocol for oral or intravenous peri-procedural hydration. Last, probably due to the relative small sample size in this study, the

double-dose group did not show significantly low incidence of CIN compared with double-dose group.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all enrolled patients included in the research.

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