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Original Article

Role of oral nicorandil in preventing contrast induced nephropathy in type 2 diabetics undergoing coronary angiography

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Abstract: Contrast induced nephropathy (CIN) remains to be a potentially serious complication following coronary angiography. CIN has become the third leading cause of hospital acquired acute renal failure. This clinical trial was performed to assess the preventive effects of oral nicorandil against CIN in type 2 diabetics undergoing coronary angiography. A total of 150 type 2 diabetics were randomly divided into three groups, basic treatment group (n=51), standard nicorandil therapy group (n=49, nicorandil 5 mg, 3 times/d were used 2 days before and 3 days after angiography), and intensive nicorandil therapy group (n=50, nicorandil 10 mg, 3 times/d were used 2 days before and 3 days after angiography). Renal functions were assessed at the time of hospital admission and on days 1, 2, and 3 after angiography. CIN occurred in 13 of 150 patients (8.67%). The incidence of CIN was lower in the nicorandil treatment groups than in the basic treatment group (8.16% vs 11.76%, 6% vs 11.76%, $P<0.05$), and a more significant decrease in the incidence of CIN in the intensive nicorandil therapy group (6% vs 11.76%, $P<0.01$). Compared with the basic treatment group, a lower proportion of patients in the nicorandil treatment groups had an eGFR decrease of 25% or greater (10.2% vs 13.73%, 8% vs 13.73%, $P<0.05$); patients with an eGFR decrease of 25% or greater accounted for an even lower proportion in the intensive nicorandil therapy group (8% vs 13.73%, $P<0.01$). Multiple Logistic Regression showed that administration of nicorandil, advanced age, lower eGFR levels, and higher dose of contrast volume were independent risk factors of CIN. In conclusion, prophylactic treatment with nicorandil in type 2 diabetics undergoing coronary angiography could effectively prevent CIN, and intensive nicorandil therapy could be more effective.

Keywords: Nicorandil, type 2 diabetes, contrast induced nephropathy, percutaneous coronary intervention

Introduction

The incidence of contrast induced nephropathy (CIN) is now increasing due to the increasing use of contrast media in percutaneous coronary intervention (PCI). CIN is an adverse event that results in increased health resource utilization, prolongs hospital stay, and increases short- and long-term mortality, even after adjustment for other co-morbidities [1]. Mohammed NM et al. [2] reported that CIN is the third leading cause of hospital-acquired renal failure, with a rate of 11%. The incidence of CIN in diabetics with preserved renal function is usually moderately increased compared with the healthy population, but diabetics with renal insufficiency have a significantly increased risk of CIN [3]. The exact pathophysiological mechanisms and optimal therapeutics of CIN remain unclear. Therefore, preventive measures for CIN are inevitable and remains a challenge among cardiologists and radiologists.

Nicorandil is an anti-anginal medication that has the dual properties of a K-ATP channel agonist and a nitric oxide (NO) donor. Recent studies revealed that nicorandil may protect the kidney from ischemic injury associated with the use of contrast media by ameliorating ischemic preconditioning [4]. As far as we know, there have been no clinical trials in the literature to evaluate the role of nicorandil in preventing type 2 diabetics from CIN. The objective of the present study was to evaluate the role of oral nicorandil for the prophylaxis of CIN in type 2 diabetics undergoing coronary angiography.

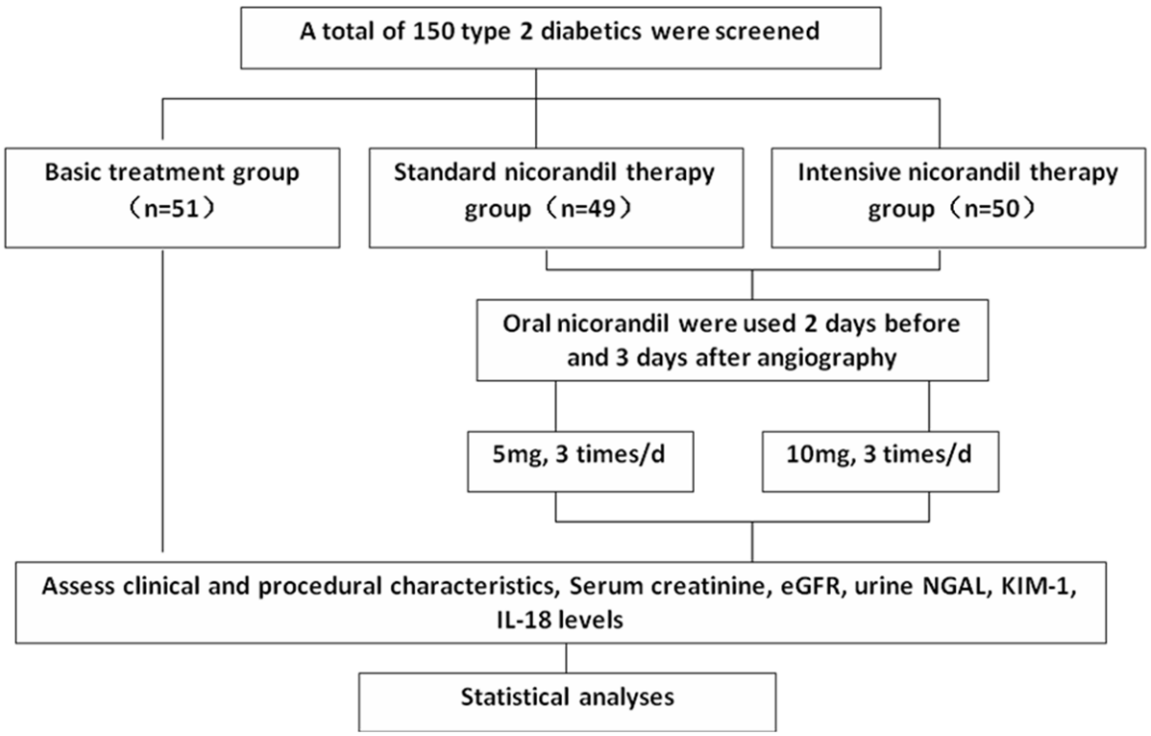

Figure 1. Randomization, study drug adherence of the study participants.

Materials and methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Tianjin Nankai Hospital (Tianjin, China), and conformed to the principles outlined in the Declaration of Helsinki. All participants were informed the details of the study and signed the written informed consents.

Study population

The present study was conducted at the Department of Cardiology at Tianjin Nankai Hospital from June 2013 to December 2015. The type 2 diabetic patients (18-80 years old) were enrolled into the current study. According to a random number table, 150 eligible patients with type 2 diabetes were divided randomly into 3 groups, basic treatment group (n=51), standard nicorandil therapy group (n=49, nicorandil 5 mg, 3 times/d were used 2 days before and 3 days after angiography), and intensive nicorandil therapy group (n=50, nicorandil 10 mg, 3 times/d were used 2 days before and 3 days after angiography) (**Figure 1**). Type 2 diabetes was defined as any of the following: fasting plasma glucose level greater than 7.0 mmol/L or a random plasma glucose level of 11.1 mmol/L or greater. Repeated measurement of fasting or random plasma glucose levels on a subsequent day was used to confirm the diagnosis of diabetes. The estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease (MDRD) equation: eGFR ($ml^{-1}*min^{-1}*1.73\ m^{-2}$)=186 × serum Cr $(mg/dl)^{-1.154}$ × age $(years)^{-0.203}$ (× 0.742 for female subjects) [5]. The exclusion criteria were patients that were hyperpyrexic or allergic to iodine or who had: tumors, severe heart failure, severe kidney failure, severe liver failure, disorders of the immune system, blood diseases.

Intervention

All patients received an intravenous infusion of 0.9% saline at a rate of 1 mL/kg/h at least 6 hours before and 12 hours after the procedure. Patients in the basic treatment group only received hydration to prevent CIN. Patients in the nicorandil group received both oral nicorandil (Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) and hydration to prevent CIN. An intravenous bolus of unfractionated heparin (70-100 U/kg) was given, and additional heparin boluses were given to maintain activated clotting time beyond 300 seconds during the procedure. The platelet glycoprotein IIb/IIIa inhibitors

Table 1. Baseline clinical and procedural characteristics of study patients

Characteristics	Basic treatment Group (*n*=51)	Standard nicorandil therapy Group (*n*=49)	Intensive nicorandil therapy Group (*n*=50)	F/X^2	*P* value
Male (%)	27 (52.94)	28 (57.14)	26 (52)	0.723	0.51
Age (y)	64.71±5.68	63.26±4.91	65.27±6.12	0.686	0.49
Age>70 yrs (%)	13 (25.49)	11 (22.45)	12 (24.0)	0.318	0.27
BMI (kg/m^2)	27.71±5.18	26.23±6.92	28.06±8.02	0.382	0.31
Hypertension (%)	33 (64.71)	31 (63.27)	34 (68)	0.117	0.18
Smoking (%)	19 (37.25)	20 (40.82)	21 (42)	0.223	0.22
Laboratory results (mmol/L)					
Total Cholesterol	4.87±1.28	4.76±1.74	4.49±1.27	0.826	0.63
Triglycerides	1.84±0.93	1.77±0.86	1.48±0.85	0.324	0.29
HDL-C	1.17±0.33	1.18±0.29	1.19±0.31	0.556	0.47
LDL-C	2.73±0.92	2.81±0.42	2.55±1.04	0.373	0.32
Fasting blood sugar	5.65±1.66	5.32±1.78	5.24±2.33	0.667	0.51
Glycosylated hemoglobin (%)	5.93±0.84	6.16±0.88	6.02±0.84	0.582	0.49
Medications (%)					
Statins	50 (98.03)	49 (100)	48 (96)	0.823	0.97
Aspirin	46 (90.20)	44 (89.79)	45 (90)	0.796	0.89
Clopidogrel	36 (70.59)	34 (69.39)	34 (68)	0.715	0.82
Beta-blocker	41 (80.39)	39 (79.59)	39 (78)	0.737	0.86
Anticoagulation	25 (60.98)	23 (58.97)	25 (62.5)	0.698	0.79
Diuretics	26 (50.98)	25 (51.02)	27 (54)	0.676	0.77
ACEI/ARB	31 (75.61)	29 (74.36)	31 (77.5)	0.812	0.91
VOCM (mL)	241.85±49.71	245.87±48.69	250.87±50.72	0.572	0.47
Hydration volume (mL)	843±158	872±137	855±141	0.589	0.51
LVEF (%)	59.26±11.62	58.73±11.85	61.32±12.08	0.613	0.55

Notes: BMI: Body Mass Index; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; VOCM: volume of contrast medium; LVEF: left ventricular ejection fraction.

were administered according to the guidelines. In addition, aspirin (100 mg/day) was continued for whole life and clopidogrel (75 mg/day) was administrated for at least 1 year unless severe bleeding complications appeared. PCI was performed by the same team in both groups. PCI were performed through the radial artery with the use of iso-osmolar nonionic contrast media iodixanol (Visipaque, 320 mg iodine/mL, GE Healthcare, Shanghai, Co., Ltd.). The volume of contrast media used was recorded for all patients during catheterization.

Outcome measures

All the tests were performed in the same laboratory with the same methodology. Serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), fasting blood sugar, and glycosylated hemoglobin, were measured at the time of hospital admission. We used the Hitachi 7600 automated biochemistry analyzer (Hitachi, Ltd., Tokyo, Japan) to test the levels of Serum creatinine (Scr). Scr and eGFR were measured at the time of hospital admission and on days 1, 2, and 3 after the procedure. The concentration of urine kidney injury molecule-1 (KIM-1), neutrophil-gelatinase-associate-lipocalin (NGAL), and interleukin-18 (IL-18) in urine were detected before and 1 day after procedure for patients in three groups. The urine levels of NGAL, KIM-1 and IL-18 were determined by enzyme-linked immunosorbent assay (ELISA) in the clinical laboratory of Tianjin Nankai Hospital.

Study end points

The primary end point of the study was the incidence of CIN, which was defined as a relative increase of ≥25% or an absolute increase of Scr ≥44.2 μmol/L compared to baseline Scr levels after PCI within 3 days.

Table 2. Changes in Scr and eGFR levels

Characteristics	Basic treatment Group (*n*=51)	Standard nicorandil therapy Group (*n*=49)	Intensive nicorandil therapy Group (*n*=50)
Scr (μmol/L)			
Baseline	83.5±18.7	82.9±19.1	84.1±19.7
Day 1 after procedure	91.5±18.7[a]	90.6±17.8[a]	88.7±19.3[a,c]
Day 2 after procedure	98.6±20.1[b]	96.7±19.3[b]	91.2±18.5[b,c,e]
Day 3 after procedure	87.8±17.6	86.9±16.7	84.5±17.1
eGFR (mL/min/1.73 m^2)			
Baseline	119.6±5.5	120.1±5.8	121.3±6.2
Day 1 after procedure	112.3±6.5[a]	114.1±6.7[a]	116.7±6.4[a,c]
Day 2 after procedure	105.2±6.3[b]	107.4±7.1[b]	110.2±6.8[b,c,e]
Day 3 after procedure	117.8±5.8	118.6±6.2	119.1±6.3
eGFR>25% decrease [n (%)]	8 (13.73)	5 (10.2)[c]	4 (8.0)[d]
Incidence of CIN [n (%)]	6 (11.76)	4 (8.16)[c]	3 (6.0)[d]

Notes: Scr: serum creatinine; eGFR: estimated glomerular filtration rate; CIN: contrast-induced nephropathy. [a]*P*<0.05, compared with baseline; [b]*P*<0.01, compared with baseline; [c]*P*<0.05, compared with basic treatment group; [d]*P*<0.01, compared with basic treatment group; [e]*P*<0.05, compared with Standard nicorandil therapy group.

The secondary end point was 25% or greater reduction in the eGFR compared to baseline, which was calculated by using MDRD equation and Scr obtained before PCI and within 3 days after PCI.

Statistical analyses

Continuous variables and categorical variables were expressed as the mean ± standard deviation (SD) and percentages, respectively. All samples were tested to ascertain if they followed a normal distribution. Categorical variables were compared using the X^2 test or the Fisher exact test where appropriate. Analysis of variance (ANOVA) was used to compare the difference of SCr, eGFR levels, and incidence of CIN before and after the procedure in each group. A Multivariate Logistic Regression model was used to identify the risk factors of CIN. The model included age, gender, eGFR, contrast volume and nicorandil. The odds ratios (OR) and their corresponding 95% confidence intervals (CI) were provided. Two-tailed *P* values P<0.05 were considered statistically significant. Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA).

Results

Safety and adverse reaction evaluation on nicorandil therapy

In the present study, no patients developed clinical renal failure or needed hemodialysis. No arrhythmia, nausea, vomiting, dizziness, palpitation, thirst, blurred vision, or retention of urine was found in the nicorandil treatment groups. Patients in the nicorandil treatment groups had no adverse reaction during the procedure.

Baseline clinical characteristics

A total of 150 eligible patients were randomized to the basic treatment group (n=51), standard nicorandil therapy group (n=49), and intensive nicorandil therapy group (n=50). Baseline clinical and procedural characteristics are listed in **Table 1**. There were no statistically significant differences in these characteristics among the three treatment groups (P>0.05).

Nicorandil influence the changes in Scr and eGFR levels

The changes in Scr and eGFR levels were listed in **Table 2**. All Scr levels were increased significantly after the procedure. The peak value occurred at day 2 and then began to decrease. The intensive nicorandil therapy group tended to have a lower Scr levels than the basic treatment group and standard nicorandil therapy group at day 2 after the procedure (91.2±18.5 vs 98.6±20.1, 96.7±19.3 μmol/L, P<0.05). There was no significant difference between the standard therapy group and the basic treatment group (96.7±19.3 vs 98.6±20.1 μmol/L, P>0.05). Scr levels were higher than baseline levels at day 3, but there was no significant difference among three groups (P>0.05).

Table 3. Changes in urine NGAL, KIM-1, and IL-18 levels

Characteristics	Basic treatment Group (*n*=51)	Standard nicorandil therapy Group (*n*=49)	Intensive nicorandil therapy Group (*n*=50)
NGAL (ng/mL)			
Baseline	7.94±4.01	7.61±3.72	7.79±3.87
Day 1 after procedure	65.61±10.72[a]	56.12±9.67[a]	40.95±8.39[a,b,c]
KIM-1 (ng/mL)			
Baseline	0.70±0.07	0.69±0.06	0.70±0.05
Day 1 after procedure	5.63±0.29[a]	4.85±0.32[a]	2.79±0.31[a,b,c]
IL-18 (ng/L)			
Baseline	42.96±5.85	41.67±4.52	40.37±4.96
Day 1 after procedure	63.15±3.51[a]	54.83±4.19[a]	45.66±4.31[a,b,c]

Notes: NGAL: urine neutrophil-gelatinase-associated-lipocalin; KIM-1: kidney injury molecule-1; IL-18: interleukin-18. [a]*P*<0.05, compared with baseline; [b]*P*<0.05, compared with basic treatment group; [c]*P*<0.05, compared with Standard nicorandil therapy group.

The eGFR levels were decreased significantly in all groups after the procedure. The eGFR levels were significantly higher in the intensive nicorandil therapy group than in the basic treatment group and standard nicorandil therapy group at day 2 after the procedure (110.2±6.8 vs 105.2±6.3, 107.4±7.1 mL/min/1.73 m^2, P< 0.05). There was no significant difference between the standard therapy group and the basic treatment group (107.4±7.1 vs 105.2±6.3 mL/min/1.73 m^2, P>0.05). The eGFR levels were lower than baseline levels at day 3 in all groups, with no significant differences among the three groups (P>0.05).

Nicorandil influence the changes in urine NGAL, KIM-1, and IL-18 levels

Within 1 day of the procedure, urine levels of NGAL (40.95±9.39 vs 65.61±10.72, 56.12± 9.67 ng/mL, P<0.05), KIM-1 (2.79±0.31 vs 5.63±0.29, 4.85±0.32 ng/mL, P<0.05), and IL-18 (45.66±4.31 vs 63.15±3.51, 54.83± 4.19 ng/L, P<0.05) in patients in the intensive nicorandil therapy group were lower than those in the basic treatment group and standard therapy group (**Table 3**). There was no significant difference between the standard therapy group and the basic treatment group in terms of urine levels of NGAL (56.12±9.67 vs 65.61±10.72 ng/mL, P>0.05), KIM-1 (4.85± 0.32 vs 5.63±0.29 ng/mL, P>0.05), IL-18 (54.83±4.19 vs 63.15±3.51 ng/L, P>0.05).

Study end points

Overall, CIN occurred in 13 of 150 patients (8.67%) (**Table 2**). The incidence of CIN in the nicorandil treatment groups was lower compared with the basic treatment group (6% vs 11.76%, 8.16% vs 11.76%, P<0.05), and a more significant decrease in the incidence of CIN in the intensive nicorandil therapy group was shown (6% vs 11.76%, P<0.01).

Compared with the basic treatment group, a lower proportion of patients in the nicorandil treatment groups had an eGFR decrease of 25% or greater (8% vs 13.73%, 10.2% vs 13.73%, P<0.05); patients with an eGFR decrease of 25% or greater accounted for an even lower proportion in the intensive nicorandil therapy group (8% vs 13.73%, P<0.01).

Results of multiple logistic regression analysis

The results of multiple logistic regression analysis indicated that administration of nicorandil (OR=0.262, 95% CI 0.086~0.772, P=0.018), advanced age (OR=8.526, 95% CI 1.949-39.387, P=0.005), lower eGFR levels (OR= 0.778, 95% CI 0.678-0.887, P=0.001), and higher dose of contrast volume (OR=5.465, 95% CI 1.728-16.953, P=0.004) were independent risk factors of CIN (**Table 4**). Nicorandil could decrease the risk of CIN. Advanced age, lower eGFR levels, higher dose of contrast volume could increase the risk of CIN.

Discussion

In the present study, we have shown that periprocedural oral nicorandil, the K-ATP channel opener, 5 or 10 mg three times per day for a short duration (beginning 2 days prior to the procedure and continuing for 3 days after it)

Table 4. Multivariate Logistic Regression analysis of CIN

Variables	OR	95% CI	*P* values
eGFR	0.778	0.678-0.887	0.001
Constrast volume	5.465	1.728-16.953	0.004
Age>70 yrs	8.526	1.949-39.387	0.005
Nicorandil	0.262	0.086-0.772	0.018
Gender	0.564	0.218-1.463	0.239
Hypertension	1.805	1.081-3.018	0.142
Smoking	1.348	1.012-3.131	0.295

Notes: CI: confidence interval; OR: odds ratio.

could reduce the incidence of CIN in patients with type 2 diabetes undergoing coronary angiography. In addition, the study demonstrated that oral nicorandil was an independent protective factor against CIN by multiple Logistic regression analysis. Therefore, what we found in this study may offer a new strategy for the prevention of CIN in type 2 diabetics.

CIN is a significant iatrogenic complication of contrast media [6]. In current clinical practice, CIN refers to an absolute increase in Scr by 0.5 mg/dl (44.2 μmol/L), or a relative 25% increase from the baseline value within 3 days after exposure to contrast medium [7]. However, it has been demonstrated that Scr does not accurately reflect renal function suffering from two important limitations. First, creatinine excreted in the urine is not solely a result of glomerular filtration but also of renal tubular secretion. This means that changes in Scr levels will underestimate the actual falling in eGFR. Second, the Scr will rise more slowly as the creatinine is distributed in whole body water. Recent studies indicate that the values of eGFR and the values of urine NGAL, KIM-1, IL-18 can specifically predict the development and progression of CIN [8, 9].

The pathophysiology of CIN is complex, multifactorial, and incompletely understood. Possible mechanisms include intrarenal vasoconstriction, reduced renal blood flow, medullary hypoxia, oxidative stress, inflammation, endothelial dysfunction, and direct tubular epithelial cell injury by contrast media [10, 11]. Many clinical observations have evaluated various agents such as N-acetylcysteine, probucol, trimetazidine, prostaglandin E1, sodium bicarbonate, dopamine, ascorbic acid, statins and cordyceps sinensis in effort to identify optimal strategies for reducing the incidence of CIN, but the results are inconsistent [12-17].

Nicorandil, a K-ATP channel opener and a NO donor, is currently used in the treatment of angina and acute heart failure. The K-ATP channels are widely distributed in various tissues, including heart, kidney and brain, could be controlled by cell metabolism via the concentration of the ATP/ADP ratio, and it is possible that they play a role in the adaptation of vascular tone to the metabolic needs and PO_2 of the tissue. Recent studies showed that activation of the K-ATP channel ameliorate ischemia-reperfusion in the kidney by preventing accumulation of reactive oxygen species (ROS) in mitochondria [18, 19]. A recent study found that nicorandil could significantly reduce the renal ischemia–reperfusion injury in rats by preventing ROS damages via down-regulating the expression of KIR6.2 in kidney [20]. In addition, another study demonstrated that nicorandil might protect the kidney from the ischemic injury associated with the use of contrast media by inducing NO production and suppressing synthesis of endothelin-1 [21]. In recent years, nicorandil has started to be used to prevent CIN, but the results are inconsistent. In the study by Fan et al. [22], 120 patients with an eGFR<60 mL/min received 10 mg nicorandil three times per day from 2 days before to 3 days after the procedure. This study demonstrated that oral nicorandil could decrease the incidence of CIN in patients with renal insufficiency undergoing elective cardiac catheterization. In another study by Ko et al. [23], 81 patients with an eGFR<60 mL/min received nicorandil 12 mg intravenously for 30 minutes prior to coronary angiography. This study showed that prophylactic intravenous infusion of nicorandil did not decrease the incidence of CIN in patients with renal dysfunction undergoing coronary angiography. However, the exact mechanisms of the effect of nicorandil on CIN are unknown and further studies are required to assess the exact mechanism.

Diabetes with pre-existing renal disease can further increase the risk of CIN. There has been little evidence regarding the effects of nicorandil on CIN in type 2 diabetics thus far. Therefore, we designed the present study to test the safety and efficacy of nicorandil on the

incidence of diabetic CIN. The protocol of our study was similar to other studies which aimed to investigate the short-term effects of medical treatments on the incidence of CIN [24, 25]. In the present study, CIN occurred in 13 of 150 patients (8.67%). The incidence of CIN in the nicorandil treatment groups was lower compared with the basic treatment group. We selected Scr, eGFR and urine levels of NGAL, KIM-1 and IL-18 after the procedure as an index of renal function. Compared with the basic treatment group, a lower proportion of patients in the nicorandil treatment groups had an eGFR decrease of 25% or greater. After the procedure, urine NGAL, KIM-1 and IL-18 levels in patients in the intensive nicorandil therapy group were lower than those in the basic treatment group and standard therapy group. Although renal function was only monitored for three days after the procedure, a beneficial effect of treatment with nicorandil is highly probable. These results strongly suggest the preventive effect of short-term nicorandil therapy on CIN in patients with type 2 diabetes who are exposed to contrast medium.

Study strength and limitations

Our study for the first time demonstrated that oral nicorandil therapy can prevent CIN in patients with type 2 diabetes undergoing coronary angiography. Hence, evidence was provided for new prevention strategies of CIN.

The present research also had several limitations. First, the study was only a single center study with a small sample size, which would have weakened the statistical power of the conclusions. Yet, statistical significance in our study was achieved despite the limited sample. Still, our data need confirmation in future studies. Second, the study cannot be extended to patients at end-stage of renal failure such as those with uremia or dialysis. Third, our data were limited to observe 3 days after angiography. Some publications have stated that Scr peaked at 3-5 days after administration of the contrast medium and returned to normal within 10 days after. Thus, this study may have missed some peak levels of Scr. However, most patients who experience the CIN usually have their Scr increased within 3 days after contrast administration, and hence most patients with CIN must have been detected in the present study. Therefore, a large well-designed trial addressing the effect of nicorandil on long-term clinical outcomes is needed before this agent could be added to the armamentarium in the prevention of CIN.

Conclusion

In conclusion, oral nicorandil was a protective factor against CIN in type 2 diabetics undergoing coronary angiography, and intensive nicorandil therapy could be more effective. Therefore, a multiple-center well-designed trial addressing the effect of nicorandil on long-term clinical outcomes is needed before this agent could be added to the armamentarium in the prevention of CIN.

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Disclosure of conflict of interest

None.

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