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Abd Elrahman Ahmed Mabrouk Ali

Faculty of Medicine, Beni-Suef University. Cardiology resident, HIO Hospital, Beni-Suef, Egypt, elgarnosy@gmail.com

Islam Shawky Abd El-Aziz Seif El-Yazal

Cardiology department, Al-Azhar University, Egypt.

Ahmed Mahmoud Mansy

Cardiology department, Al-Azhar University, Egypt.

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Role of Nicorandil Effect on Contrast-induced Nephropathy in Patients Land for Elective Percutaneous Coronary Intervention

Abd Elrahman Ahmed Mabrouk Ali ^{a,*},
Islam Shawky Abdelaziz ^b, Ahmed Mahmoud Mansy ^b

^a Resident of Cardiology, HIO Hospital, Beni-Suef, Egypt

^b Department of Cardiology, Al-Azhar University, Cairo, Egypt

Abstract

Background: Patients having percutaneous coronary intervention (PCI) and coronary angiography are more likely to experience contrast-induced nephropathy (CIN), which is linked to higher mortality and morbidity (PCI). Our goal was to assess the effectiveness of nicorandil medication given to patients getting ready for elective PCI in reducing the occurrence of CIN.

Methods: Four hundred eligible patients in total were included in the trial and divided into the control ($n = 200$) and nicorandil ($n = 200$) groups. Patients in the nicorandil group were given 10 mg of nicorandil twice (oral) beginning one week before and continuing orally with the same dose for two days after an elective PCI in addition to the conventional hydration therapy. Serum creatinine (SCr) levels were assessed 24 h prior to and 48 h following the procedure.

Results: The mean baseline creatinine level among patients in the Nicorandil group was 1.064 ± 0.34 and that for patients in the control group was 1.11 ± 0.31 (P value = 0.150). After the procedure, the mean creatinine level was 1.097 ± 0.34 in the Nicorandil group and 1.25 ± 0.52 in the control group with statistically significant difference (P value = 0.003). There was a significant higher creatinine level after the procedure in both groups but, the increase was more in the control group than Nicorandil group. In the control group, the serum creatinine (SCr) increased from 1.111 ± 0.31 to 1.25 ± 0.52 , while in the Nicorandil group increased from 1.064 ± 0.34 to 1.097 ± 0.34 (P value < 0.001). In addition, there was a significant higher percentage of increase of creatinine in the control group than the Nicorandil group.

Conclusions: In individuals receiving an elective cardiac intervention, Nicorandil may have a protective effect against CIN and lessen adverse outcomes.

Keywords: Contrast, Induced, Nephropathy, Nicorandil, PCI

1. Introduction

Contrast-induced nephropathy (CIN), a severe form of kidney damage brought on by the use of iodine-containing contrast agent, has become a frequent complication in the treatment of coronary artery disease, which raises morbidity and mortality throughout the follow-up periods.¹

CIN increases morbidity, lengthens hospital stays, and hence raises health care expenses. CIN can

occur in 2 percent to 30 percent of people. Fortunately, the majority of cases may be fully cured in two to four weeks. It is still unclear what the best treatments are for preventing CIN.²

Kidney functions are quite helpful in predicting the incidence of CIN before contrast medium is administered. Age, chronic renal disease, and diabetes mellitus are a few of the risk factors that contribute to the development of CIN.³

In this regard, nicorandil, a nitrate-containing adenosine triphosphate-sensitive potassium (KATP)

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* Corresponding author at: Beni-Suef University, Cardiology resident, HIO Hospital, Beni-Suef, Egypt. Tel. +01120058200, Fax: 2110009. E-mail address: elgarnosy@gmail.com (A.E. Ahmed Mabrouk Ali).

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channel opener, may be a promising treatment approach for both patients and doctors.⁴

The cardio-protective properties of nicorandil have been well documented; however, the reno-protective potential has received less attention and has produced conflicting results, particularly in elective PCI.⁵

So, the aim of this study was to evaluate the preventive efficacy of peri-procedural treatment of nicorandil against the incidence of CIN in patients prepared for elective PCI.

2. Patients and methods

After receiving clearance from the regional institutional ethics committee and regional institutional review board, this study was carried out at the Al-Azhar University Hospital. A randomized controlled clinical trial was used for the investigation. Before being enrolled and randomly assigned, the qualified patients gave a thorough informed consent.

The study's researchers unsealed the separate, opaque envelopes with the computer-generated random numbers shortly before to tracheal intubation. For reporting randomized, controlled clinical studies, the Consolidated Standards of Reporting Trials guidelines were adhered to.

The research comprised adults aged more than 18 years who underwent elective PCI. ACS-PCI or non-elective PCI, allergy to contrast dye or nicorandil, recent exposure to nicorandil or contrast medium, pregnancy, left ventricular ejection fraction 30 percent by echocardiogram or evident by pulmonary edema, Acute or advanced chronic kidney diseases with estimated eGFR<15 ml/min, history of kidney transplantation were the exclusion criteria.

The patients were prospectively randomized into two groups for conventional therapy of coronary heart disease and one for nicorandil treatment, which involved receiving 10 mg of nicorandil twice (oral) beginning one week before and continuing orally with the same dose for two days after the procedure.

All regular tests were carried out after admission, with a focus on echocardiography, myocardial damage marker measurement, and renal function indicators. Before and following nicorandil medication, peripheral venous blood serum and urine samples were taken, while the patient was fasting.

The development of CIN is defined as an increase in SCr level at 44.2 $\mu\text{mol/l}$ (0.5 mg/dl) or 25% above the baseline within 72 h after contrasting medium administration without an alternative cause.

All patients received guidelines-directed treatment for the underlying cardiac diseases and the

standard measures to prevent CIN. These measures included general supportive care (oxygen inhalation, maintaining a comfortable body position, or sedation); cardiotoxic, diuretic, vasodilator, anti-platelet, anticoagulation, and improvement of coronary circulation; prognosis improvement (beta blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/and aldosterone receptor antagonist); and improvement of renal function and maintenance.

The nicorandil group also received nicorandil at a dose of 10 mg of nicorandil twice (oral) beginning one week before and continuing orally with the same dose for two days after the procedure (oral nicorandil tablets were acquired as Adancor 10 mg tablets provided by Merck Pharmaceutical firm). This is the recommended dosage of nicorandil for the treatment of heart failure in our department.

SPSS v. 25 (Statistical Package for Social Science) for Windows was used to analyze the data. Mean and standard deviation were used to describe quantitative variables (SD). The qualitative factors were described using numbers (No.) and percentages. To establish a link between normally distributed variables, Pearson correlation was utilized. The significance of the results was evaluated using a *P*-value, which was classified as non-significant when *P*-value was greater than 0.05 and significant when *P*-value was less than 0.05.

3. Results

Table 1 showed that there was insignificant difference between both groups regarding their baseline characteristics (both groups were matched).

Table 2 showed that there was a significant higher creatinine level after the procedure in both groups but, the increase was more in the control group (the difference was 0.14 ± 0.3) than Nicorandil group (the difference was 0.03).

Table 1. Baseline characteristics in the studied groups.

Items	Control group (no = 200)	Nicorandil group (no = 200)	<i>P</i> value
Age (years) (Mean \pm SD)	59.7 \pm 5.8	60 \pm 8.7	0.627
Sex			
Males	80 (40%)	87 (43.5%)	0.650
Females	120 (60%)	113 (56.5%)	
DM	73 (36.5%)	83 (41.5%)	0.305
HTN	84 (42.0%)	103 (51.5%)	0.057
EF % (Mean \pm SD)	55.8 \pm 7.5	55.5 \pm 6.1	0.846
Creatinine (mg/dl) (Mean \pm SD)	1.111 \pm 0.31	1.064 \pm 0.34	0.150
Amount of dye (ml) (Mean \pm SD)	154.1 \pm 54.1	162.6 \pm 59.6	0.138

Table 2. Follow up the creatinine level in the studied groups (pre-post intervention).

Creatinine (mg/dl)	Control group (no = 200)	Nicorandil group (no = 200)	P value
Pre	1.111 ± 0.3 1	1.064 ± 0.34	0.150
Post	1.25 ± 0.52	1.097 ± 0.34	0.003*
Mean difference	0.14 ± 0.3	0.03 ± 0.05	
P value (pre-post in each group)	<0.001*	<0.001*	

*P-value is significant.

Table 3 showed that the percent of the increase in creatinine was significantly higher in the control group than the Nicorandil group. However, the incidence proportion of contrast-induced nephropathy didn't differ significantly between both groups, the incidence was lower (1%) in the Nicorandil group then the control group (3%).

Table 4 showed that in the Nicorandil group, there was a significant weak positive linear correlation between the amount of dye and the percent of the increase of creatinine after the intervention. In addition, there was a significant weak positive linear correlation between age and creatinine after the intervention. In the control group, there was a significant weak positive linear correlation between the age and percent of the increase of creatinine and creatinine after the intervention.

There was no significant association between DM and creatinine level after intervention or its percentage of increase in drug groups but there was a significant relation with DM in the control group of creatinine after intervention, but the percent of increase didn't differ significantly. There was a significant association between the higher creatinine level after the intervention and hypertension in Nicorandil group, but this didn't affect the percentage of increase significantly. There was no significant association between HTN and creatinine

Table 3. Percentage of increase of creatinine and incidence of contrast-induced nephropathy in the studied groups.

Creatinine (mg/dl)	Control group (no = 200)	Nicorandil group (no = 200)	P value
Percentage of increase			
Mean ± SD	13.7 ± 30.4	3.1 ± 4.9	<0.001*
Median (IQR)	8.3 (12.5, 1)	0.9 (4.1–0)	
Contrast-induced nephropathy	6 (3%)	2 (1%)	0.284 (FET)

P value is significant.

FET, Fisher exact test; IQR, interquartile range.

Percentage of increase = [(Post-Pre)/Pre] X100.

N.B. Values with negative signs indicate postintervention increase of creatinine.

Table 4. Correlation between age and amount of dye and creatinine after the procedure and percent of the increase of creatinine in Nicorandil and control groups.

Items	Nicorandil group		Control group	
	Age	Amount of dye	Age	Amount of dye
Percent of increase of creatinine				
R	0.021	0.223	0.148	0.076
P-value	0.768	0.002*	0.036*	0.283
Post creatinine				
R	0.272	-0.025	0.382	0.107
P value	<0.001*	0.759	<0.001*	0.193

*P value is significant.

level after intervention or its percentage of increase in the control group (Table 5).

4. Discussion

Contrast-induced nephropathy has emerged as one of the major contributors to iatrogenic renal insufficiency as a result of the expanding use of medical imaging contrast agents. On renal tubular epithelial cells and vascular endothelial cells, contrast agents exert direct cytotoxic effects that cause swelling, vacuolization, apoptosis, and eventually necrosis.⁶

A typical technique for treating and diagnosing coronary heart disease is percutaneous coronary intervention (PCI). However, the use of contrast agents during PCI typically results in contrast-induced nephropathy (CIN).⁷

In patients having coronary angiography or percutaneous coronary intervention, nicorandil can considerably lower the incidence of contrast-induced nephropathy or offer renal protection for those with chronic kidney disease.⁸

This study was carried out at Al-Azhar University hospital after obtaining approval from the local research ethical committee. The study was performed on 400 patients of both sexes to evaluate the preventive efficacy of pre-procedural treatment of nicorandil against the incidence of CIN in patient prepared for elective PCI.

This study showed that, there was a significant higher creatinine level after the procedure in both groups but the increase was more in the control group (the difference was 0.14 ± 0.3) than the Nicorandil group (the difference was 0.03 ± 0.05). In addition, there was a significant higher percentage of increase of creatinine in the control group than the Nicorandil group.

The mean baseline creatinine level among patients in the Nicorandil group was 1.064 ± 0.34 mg/dl and that for patients in control group was 1.111 ± 0.31 mg/dl. After the procedure, the mean

Table 5. Association between diabetes mellitus and hypertension and creatinine postintervention and percentage of increase of creatinine in each group.

Group	N	Mean	SD	P value
CONTROLS				
Post creatinine				
No DM	127	1.1909	0.42242	0.029*
DM	73	1.3586	0.65531	
Percent of increase of creatinine				
No DM	127	-10.5845	28.42561	0.273
DM	73	-14.8886	23.31508	
CASES				
Post creatinine				
No DM	117	1.0558	0.31194	0.050
DM	83	1.1552	0.38901	
Percent of increase of creatinine				
No DM	117	-3.1277	5.18180	0.597
DM	83	-3.5025	4.56304	
CONTROLS				
Post creatinine				
Not HTN	116	1.2238	0.45373	0.370
HTN	84	1.2913	0.60925	
Percent of increase of creatinine				
Not HTN	116	-10.8226	29.43434	0.408
HTN	84	-13.9961	22.40992	
CASES				
Post creatinine				
Not HTN	97	1.0082	0.15183	0.001*
HTN	103	1.1807	0.44807	
Percent of increase of creatinine				
Not HTN	97	-3.9400	5.21167	0.067
HTN	103	-2.6648	4.58060	

*P-value is significant.

DM, diabetes mellitus; HTN: hypertension; SD, Standard deviation.

creatinine level was 1.097 ± 0.34 mg/dl in the Nicorandil group and 1.25 ± 0.52 mg/dl in the control group. There was insignificant difference between both groups regarding their baseline creatinine level. However, there was a significant higher creatinine level in the control group after the procedure.

Similar results were reported by Zeng et al. (2019) in their study about the preventive role of nicorandil on CIN after cardiac catheterization. They showed that there were no significant variations in SCr between the intervention groups and the control group at the beginning of PCI. SCr were greater than baseline in both the nicorandil groups and the control group 48 h after the procedure. Post-procedure, it was considerably lower in the nicorandil groups as compared to the control group.⁹

Similar to this, Nawa et al. (2015) showed in their study that patients in the nicorandil group had substantially lower rises in blood creatinine than the control group after 24 h following PCI. In the control group, the rate of increase in SCr levels rose progressively. The percentage increase in SCr in the

nicorandil group, however, remained almost unchanged from baseline.¹⁰

Additionally, Yi et al. meta-analysis's of the effectiveness and safety of nicorandil in preventing Contrast-Induced Nephropathy following elective Percutaneous Coronary Intervention (2020) discovered that nicorandil could lower the incidence of CIN without raising the risk of major adverse events following elective PCI. Furthermore, the effectiveness of nicorandil in reducing the incidence of CIN is unaffected when administered intravenously or orally.⁴

The pathogenesis of CIN may be influenced by a number of mechanisms as a result of the medullary hypoxia, including the direct cytotoxic effects of contrast media on renal epithelial cells due to its high osmolality, activated tubule-glomerular feedback, impaired production of nitric oxide, adenosine, endothelin, prostaglandin, and angiotensin, as well as increased renal interstitial pressure.¹¹

The etiology of CIN is thought to include the interaction of ischemia, an inflammatory response, and damage brought on by free radicals with contrast-mediated vasoconstriction of the renal vasculature.¹²

Additionally, Morcos et al. (2019) research showed that the issue is directly linked to alterations in renal hemodynamics, toxic damage to renal tubular epithelial cells, a decline in nitric oxide production, intracellular calcium excess, and oxidative stress.¹³

A synthetic ATP-sensitive potassium channel opener and nitric oxide donor, nicorandil, can enhance cardiac sympathetic nerve activity, microvascular circulation, and left ventricular function.¹⁴

By offering ischemia preconditioning, vasodilation, and suppression of free radical-induced damage, the protective mechanisms may be implicated in the renal vasculature, resulting in an amelioration of CM-induced damage. Such measures lessen renal ischemia and injury, which may lower the risk of CIN.¹⁵

Nicorandil works by allowing the kidney's K-ATP channel to open. Increased renal blood flow and decreased kidney damage from oxygen-free radicals brought on by hypoxia can both be achieved by opening K-ATP channels in the kidneys. According to studies, nicorandil lessens renal ischemia-reperfusion damage by suppressing the expression of the K-ATP subunit KIR 6.2 in the kidney, which prevents the formation of oxygen-free radicals.⁶

Additionally, it encourages the endogenous ischemic preconditioning system, which makes tissues more tolerant to ischemia. Ischemic preconditioning using a remote approach has recently been demonstrated to lower the incidence of CIN.¹⁵

According to Tamura et al. (2012), nicorandil can ameliorate renal damage and decrease urine protein synthesis by suppressing the oxidative stress response in renal insufficiency.¹⁶

Regarding the baseline characteristics of patients under the study, our results showed that the mean age of patients received nicorandil before PCI was 60 ± 8.7 years and most of them were females (56.5%). The mean value of Ejection Fraction among patients in the Nicorandil group was 55.5 ± 6.1 and in the control group 55.8 ± 7.5 . The mean amount of dye injected was 162.6 ± 59.6 ml for patients in the Nicorandil group and 154.1 ± 54.1 ml for the control group. There was insignificant difference between both groups regarding their age, sex, EF, and the amount of dye injected the amount of dye.¹⁶

Similar findings were reported by Iranirad et al. (2017) who revealed that the mean age of patients in the nicorandil group was 61.35 ± 11.77 and the majority of them were males in their research on the efficacy of nicorandil therapy for prevention of contrast-induced nephropathy (60.9 percent).¹⁷

Additionally, Zhang et al. (2020) demonstrated that there were no discernible variations in age or gender between the two groups in their investigation on the effectiveness of nicorandil in the treatment of contrast-induced nephropathy. The majority of the patients were men, with a mean age of 62.25 ± 16.63 (59.84 percent).⁶

Zhang et al. (2020) revealed in their study about the efficacy of nicorandil on the prevention of contrast-induced nephropathy that the mean left ventricular ejection fraction was 51.39 ± 10.35 for patients in the nicorandil group and 53.58 ± 12.77 for patients in the control group with no significant differences between both groups.⁶

Also, the study of Andò et al. (2013) about contrast-induced nephropathy in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention showed that the mean ejection fraction of patients was 48.6 ± 11 .¹⁸

Fan et al. (2016) in their study about the preventive effect of oral nicorandil on contrast-induced nephropathy. They revealed that the dose of dye used was 145.3 ± 51.6 for patients in the nicorandil group and 149.2 ± 57.0 for the control group.¹¹

Also, Nawa et al. (2015) had the same results and demonstrated that the amount of dye used was 135.2 ± 57.0 for patients in the nicorandil group and 146.3 ± 63.6 for the control group. Both of these volumes were kept relatively small because the patients in both groups were known to have a poor renal function, which was apparent from the high SCr levels and low estimated GFRs.¹⁰

Although, more complex coronary interventions invariably used higher volumes per procedure. In the study of Batra et al. (2018) the amount of contrast used was 178 ± 27.76 in patients who developed CIN and 162.77 ± 32.07 for control groups.¹⁹

In the current study, the most common co-morbidities of ischemic heart diseases are DM and HTN. This study showed that of patients in the Nicorandil group 51.5% were hypertensive and 41.5% were diabetics. There was insignificant difference between both groups regarding their co-morbidities of clinical importance distribution.

There was no significant association between DM and creatinine level after intervention or its percentage of increase in the nicorandil group but there was a significant relation with DM in the control group of creatinine after intervention, but the percent of increase did not differ significantly. There was a significant association between the higher creatinine level after the intervention and hypertension in the Nicorandil group, but this didn't affect the percentage of increase significantly. There was no significant association between HTN and creatinine level after intervention or its percentage of increase in the control group.

The meta-analysis performed by Li et al. (2018) on the preventive role of nicorandil in reducing the incidence of CIN showed near results. They revealed that hypertension was the most common co-morbidity followed by diabetes mellitus.²⁰

In addition, Iranirad et al. (2017)'s study on the effectiveness of nicorandil treatment for preventing contrast-induced nephropathy in high-risk patients undergoing cardiac catheterization revealed that hypertension was the most prevalent comorbidity, affecting 54.7% of cases, followed by diabetes mellitus, affecting 42.2% of cases.¹⁷

In type 2 diabetics having coronary angiography, Zhao et al. (2016)'s investigation on the use of oral nicorandil to avoid contrast-induced nephropathy demonstrated that the risk of CIN is significantly increased when there is already pre-existing renal impairment.²¹

Similar to this, Batra et al. (2018)'s investigation on the risk factors for contrast-induced acute kidney damage (CIN) revealed a substantial correlation between CIN and diabetes mellitus and hypertension.¹⁹

4.1. Limitation

Our study had some limitations as being uni-centric and not double-blinded and used one dose for the interventional arm and this lack of

adjustment for doses. More kidney function tests may be needed.

5. Conclusion

The current study demonstrates that nicorandil protects nephrons against contrast-induced nephropathy in individuals having an elective cardiac intervention and may be useful in lowering the frequency of adverse events following the treatment.

Conflicts of interest

None declared.

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