ISSN 2515-8260 Volume 08, Issue 03, 2021

The Predictive Value of Oral Nicorandil on Contrast Induced Nephropathy in Patients with Renal Insufficiency Undergoing Cardiac Catheterization in Non ST Segment Elevation Acute Coronary Syndrome

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Abstract

Background

CIN leads to increased morbidity, prolonged hospital stay and thereby, more health care costs. The incidence of CIN varies from 2% to 30%. Fortunately, most cases can be completely reversed within two to four weeks. The optimal therapeutics used to prevent and CIN remains unclear. The main objective of the current study is to assess the effect of oral Nicorandil on the occurrence of CIN in patients with renal insufficiency undergoing cardiac catheterization in NSTEACS.

Results

A prospective study included 100 eligible patients allocated to either the Nicorandil group (n = 50) or the control group (n = 50). Nicorandil group received 20 mg Nicorandil daily (10 mg BID) from 1 day before to 3 days after the procedure with standard intravenous saline hydration for 12 hours before and after the procedure,

ISSN 2515-8260 Volume 08, Issue 03, 2021

whereas control group received intravenous hydration only via the same protocol. Serum creatinine and creatinine clearance were measured 24 hours before and (24 hours, 72 hours and 1 week) after the procedure. The eGFR was calculated using the Cockcroft-Gault formula.

There was a significant difference as regards CIN occurrence between both groups ,28% in control group and12% in the Nicorandil group.

Conclusion

The main finding is that in patients with renal impairment, undergoing cardiac catheterization in the setting NSTACS, Nicorandil and adequate hydration is an effective and safe strategy for decreasing the occurrence of CIN in comparison with hydration.

Key Words; Oral Nicorandil, CIN, Cardiac Catheterization, Renal Insufficiency, NSTACS.

Background

Contrast induced nephropathy (CIN) is defined as an elevation of serum creatinine level 44.2 μmol/l (0.5 mg/dl) or 25% above the baseline within 48–72 hours after contrast administration without an alternative cause. **(1)**

CIN can be attributed to intrarenal vasoconstriction, with more frequent incidence in impaired kidneys rather than normal ones. Iodinated CM was considered to cause CIN by affecting renal blood flow and vascular resistance in impaired kidneys. **(2)**

The risk of CIN rises in chronic kidney disease (CKD) patients, which is defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min per 1.73 m^2. Certain precautions should be followed before patient exposure to contrast. **(3)**

Comparing outcomes between CKDpatients planned for coronary revascularization and CKD patients managed medically only, long-term survival in patients with renal impairment (eGFR <60 ml/min/1.73 m2) treated by revascularization versus medical treatment had the best overall long-term survival with CA and subsequent PCI. (**4)**

The diagnosis and management of acute coronary syndromes have progressed significantly. New antithrombotic agents have improved the results of medical treatment and new methods of estimating a patient's risk of an adverse outcome help clinicians to decide who may benefit from invasive treatment that is, CA (CA) and subsequent revascularization either by percutaneous coronary intervention (PCI) or coronary bypass surgery. **(5)**

As these therapeutic decisions need to be made soon after admission, the categorization of acute coronary syndromes is now based on the information that is available on admission. If no ST segment elevations are present (normal or depressed ST segments or T wave inversion), a diagnosis non ST elevation acute coronary syndrome is made.**(6)** NSTACS includes NSTEMI and unstable angina which are very similar, with NSTEMI having positive cardiac biomarkers**. (7)**

Several strategies, such as hydration, N-Acetylcysteine, Sodium Bicarbonate, Statins, B-type Natriuretic Peptide, Fenoldopam and Dopamine have been used to prevent and minimize this complication. However, the optimal therapeutics remain unclear. **(8)**

Many researches have demonstrated that Nicorandil represents significant cardio protective effects in primary and elective PCI. Nevertheless, few reports were available about preventive role of Nicorandil on CIN. Recent basic studies showed that Nicorandil could enhance ischemia–reperfusion injury in the mouse kidney by guarding against tubule damage and decreasing accumulation of reactive oxygen products. **(9)** Nicorandil has vasodilatory effect, anti-inflammatory effect, ischemic preconditioning effect, prevention of microvascular vasospasm, antiarrhythmic effect and enhancement of microcirculation through (K-ATP channel). **(10)**

As a Nitric Oxide donor, Nicorandil counteracts intracellular oxygen free radicals, increases renal blood flow and decreases inflammatory reaction**. (11)** It induces hyperpolarization of mitochondrial membrane through opening of intracellular K+ATP channels. Also, it inhibits the opening of T Type Calcium channel. **(12**) Nicorandil can decrease cardiac biomarkers, such as CK-MB and TnT after elective PCI. **(13)**

Many studies focused on prevention of peri-procedural myocardial damage, through medical treatment. **(14)** Standard medical regimen used in ischemic patients includes antiplatelets , anticoagulants, statins, beta blockers and CCBs . However, myocardial damage occurs in patients after PCI, which seriously affects the patient's heart function and prognosis. Therefore, enhancing the blood flow perfusion and decreasing ischemia of the myocardium is vital. Research has highlighted Nicorandil role in decreasing arrhythmia, anginal pain and re-flow phenomenon caused by PCI. **(15)** Nicorandil also appears to have a protective impact on endothelial function and might help to stabilize coronary plaque**. (16)**

Many trials discussed the role of Nicorandil in enhancing long-term clinical outcomes. This potential benefit was first discussed by the Impact of Nicorandil in Angina (IONA) study. (13) In IONA, 5126 patients with stable coronary artery disease were allocated to take either 20 mg of Nicorandil or placebo. Significant decline was noted in the composite end point of death due to coronary heart disease, non-fatal myocardial infarction or unplanned hospital admission with chest pain in the treatment group. **(17)**

ISSN 2515-8260 Volume 08, Issue 03, 2021

The main objective of this study is to assess the effect of oral Nicorandil on the occurrence of CIN in patients with renal insufficiency undergoing cardiac catheterization in non ST elevation acute coronary syndrome setting (NSTEACS).

Methods

This prospective study was carried out at the hospital in the period between 5/2019 and 12/2020

A. Patients: All patients gave consent before being included in the procedure.

Patients subdivided into two groups:

Nicorandil group: Including 50 patients received Nicorandil and standard intravenous hydration.

Control group: Including 50 patients received standard intravenous hydration only.

Inclusion criteria: Patients diagnosed as NSTEACS (except very high risk group), age of 20 years or older, patients with renal impairment which defined as eGFR ≤60 mL/min/1.73 m^2 with Mehran CIN risk score in the low risk and intermediate risk zone.

Exclusion criteria: Patients diagnosed as very high NSTEACS, end-stage renal insufficiency (eGFR < 15 mL/min), patients with Mehran CIN risk score in the high risk and very high risk zone, acute renal insufficiency, pregnancy, lactation, cardiogenic shock, pulmonary edema, and multiple myeloma, history of an allergic reaction to contrast agents or Nicorandil, CM administration within 1 week before the CA. Uremia and renal failure which ended with dialysis.

The administration of N-acetyl cysteine, metformin, dopamine, theophylline, sodium bicarbonate, mannitol, fenoldopam, diuretics and nephrotoxic medicines within 48 hours before the procedure. ST elevation AMI, new onset bundle branch block and patients with stable coronary artery disease.

B. Methods

Checklist for assessment of all the data relevant to the patients were did. On admission, the patients were subjected to the following after a written informed consent.

A-Full history and demographic data: used to collect data of study subjects. It includes questions concerning age, sex, education grade, marital status, employment status,

economic status) and clinical history (chest pain, Hypertension, DM, smoking, drug dependency, body mass index, smoking history).

B- Investigations

•Serum creatinine: serum creatinine and eGFR in predicting kidney disease progression and cardio-renal outcomes in patients. **(18)**

•The Estimated Glomerular Filtration Rate: The eGFR was estimated using the Cockcroft-Gault formula, (140 – age) weight [kg]/ (Serum creatinine× 72) in male patients with adjustment for female patients multiplied by 0.85. The kidney function was categorized according to the stages set by the United States National Kidney Foundation and defined by the eGFR value as follows: normal kidney function: GFR ≥ 90 mL/min/1.73 $m^2$and no proteinuria; mild kidney damage: GFR of 60–89 mL/min/1.73 m^2, with evidence of kidney damage; moderate damage: GFR of 30–59 mL/min/1.73 m^2; severe damage: GFR of 15–29 mL/min/1.73 m^2; and kidney failure (dialysis): GFR < 15 mL/min/1.73 m^2. **(19)**

•Cardiac Biomarker: As non ST elevation acute myocardial infarction (NSTEMI) seems to be rising. Among the NSTE-ACS, the presence of more sensitive cardiac biomarker assays, in particular cardiac-specific troponin, has led to increased detection of NSTEMI. **(20)**

• Electrocardiography: Although, the sensitivity of the ECG is not high, it remains an important tool to assist in a rapid establishment of the working diagnosis of ACS. **(21)**

•Echocardiographic evaluation: NSTEMI can be accurately diagnosed in more than 90% of patients by echocardiography. This can accelerate starting of appropriate treatment on time and thereby decrease morbidity and mortality. **(22)**

C. Procedure related protocol:

A total of 100 eligible patients were randomly allocated to either the Nicorandil group (n = 50) or the control group (n = 50). Nicorandil group received 20 mg Nicorandil daily (10 mg BID) from 1 day before to 3 days after the procedure with standard intravenous hydration (1 mL/kg/h) via normal saline, a maximum 100 mL/h (0.5 mL/kg/h in cases of left ventricular ejection fraction [LVEF] <40%) for 12 hours before and 12 hours after the procedure, whereas control group received intravenous hydration only via the same protocol.

Serum creatinine levels and creatinine clearance were measured 24 hours before, (24 hours, 72 hours and 1 week) after the procedure. Several parameters were analyzed in the

overall population. The eGFR was calculated using the Cockcroft-Gault formula, (140 – age) × weight [kg]/ (Serum creatinine× 72) in male patients with modification for female patients multiplied by 0.85. No significant difference was detected between the two groups as regards to number of patients taking ACEI, beta blockers or statins during hospitalization.

Results

This study was conducted on 100 patients with renal insufficiency undergoing CA in non ST acute coronary syndrome setting. Patients were randomized into two groups, each group was 50 patients, according to the administration of Nicorandil 20 mg (10mg BID) from 1 day before to 3 days after the procedure in addition to standard saline hydration hydration (1 mL/kg/h) via normal saline, a maximum 100 mL/h (0.5 mL/kg/h in cases of left ventricular ejection fraction [LVEF] <40%) for 12 hours before and 12 hours after the procedure in Nicorandil, whereas control group received intravenous hydration only via the same protocol.

Both groups were compared regarding the demographic data, family history of coronary artery disease, chest pain onset before admission, clinical examination, echocardiography, angiographic finding, contrast type, contrast amount, serum creatinine and creatinine clearance before the procedure, 24 hours, 72 hours and 1 week after the procedure and the development of CIN after the injection of CM.

Table (1): Demonstrated comparison between both groups Nicorandil group and control group as regards age, gender and weight.

Table (1): Comparison between both groups Nicorandil group and control group as regards age, gender and weight.

		Control group	Nicorandil group	Test value	P-value	Sig.
		No. = 50	No. = 50			
Age (years)	Mean ± SD	64.16 ± 7.66	61.30 ± 8.73	1.741•	0.085	NS
	Range	49 – 80	43 – 80			
Gender	Males	30 (60.0%)	27 (54.0%)	0.367*	0.545	NS
	Females	20 (40.0%)	23 (46.0%)			
Weight (kg)	Mean ± SD	77.18 ± 10.04	78.52 ± 14.66	-0.533•	0.595	NS
	Range	60 – 96	23 – 100			

No statistical difference was found between control group and Nicorandil group as regards age (64.16 ± 7.66 vs 61.30 ± 8.73 years, P=0.085), gender (30 males (60%) and 20 females (40%) control group, 27 males (54%) and 23 females (46%) Nicorandil

group, P= 0.545) and weight (77.18 ± 10.04 control group vs 78.52 ± 14.66 in Nicorandil group, P=0.598).

Table (2): Comparison between both groups Nicorandil group and control group as regards smoking status, family history of premature CAD, prior MI, prior angina, prior PCI, prior CABG, type I DM, type II DM, hypertension, dyslipidemia, PVD and CVS.

		Control group No. = 50	Nicorandil group No. = 50	Test value	P-value
Smoking status	Yes	26 (52.0%)	31 (62.0%)	1.020*	0.313
	No	24 (48.0%)	19 (38.0%)		
Family history	Yes	21 (42.0%)	10 (20.0%)	5.657*	0.017
	No	29 (58.0%)	40 (80.0%)		
Prior MI	Yes	11 (22.0%)	10 (20.0%)	0.060*	0.806
	No	39 (78.0%)	40 (80.0%)		
Prior Angina	Yes	18 (36.0%)	14 (28.0%)	0.735*	0.391
	No	32 (64.0%)	36 (72.0%)		
Prior PCI	Yes	11 (22.0%)	8 (16.0%)	0.585*	0.444
	No	39 (78.0%)	42 (84.0%)		
Prior CABG	Yes	2 (4.0%)	0 (0.0%)	2.041*	0.153
	No	48 (96.0%)	50 (100.0%)		
Type I DM	Yes	0 (0.0%)	1 (2.0%)	1.010*	0.315
	No	50 (100.0%)	49 (98.0%)		
Type II DM	Yes	25 (50.0%)	24 (48.0%)	0.040*	0.841
	No	25 (50.0%)	26 (42.0%)		
Hypertension	Yes	34 (68.0%)	37 (74.0%)	0.437*	0.509
	No	16 (32.0%)	13 (26.0%)		
Dyslipidemia	Yes	18 (36.0%)	26 (52.0%)	2.597*	0.107
	No	32 (64.0%)	24 (48.0%)		
PVD	Yes	0 (0.0%)	3 (6.0%)	3.093*	0.079
	No	50 (100.0%)	47 (94.0%)		
CVS	Yes	2 (4.0%)	2 (4.0%)	0.000*	1.000
	No	48 (96.0%)	48 (96.0%)		

No statistical difference was found between control group and Nicorandil group as regards smoking (52 % were smokers in control group and 62% in Nicorandil group, P=0.313). However, there was a significant difference among both groups as regards family history (21 (42%) in control group vs 10 (20%) in Nicorandil group, P=0.017).

No statistical difference was found between control group and Nicorandil group as regards prior MI, prior angina, prior PCI, prior CABG, type I DM and type II DM, hypertension, dyslipidemia, PVD, CVS and chest pain onset before admission.

Table (3): Comparison between both groups Nicorandil group and control group as regards serum creatinine levels and creatinine clearance measured 24 hours before, 24 hours after the procedure, 72 hours after the procedure and 1 week after the procedure

		Control group	Nicorandil group	Test value	P-value
		No. = 50	No. = 50		
Creat. before procedure	Mean ± SD	1.61 ± 0.18	1.65 ± 0.22	-0.939•	0.350
	Range	1.1 – 1.9	1.1 – 2.3		
Cr.clearance before procedure	Mean ± SD	47.00 ± 8.70	48.65 ± 9.60	-0.900•	0.370
	Range	29.58 – 74.44	12.46 – 62.5		
S.creat after 24 hours	Mean ± SD	1.84 ± 0.34	1.79 ± 0.31	0.736•	0.464
	Range	1.2 – 2.7	1.1 – 2.7		
Clearance 24 hrs after	Mean ± SD	42.47 ± 10.38	45.78 ± 12.59	-1.436•	0.154
	Range	20.12 – 74.44	11.33 – 74.07		
Cr.72hrs after	Mean ± SD	1.93 ± 0.54	1.80 ± 0.76	0.968•	0.335
	Range	1.3 – 4	1.1 – 6.5		
Clearance 72 hrs after	Mean ± SD	41.72 ± 12.16	47.88 ± 14.74	-2.282•	0.025
	Range	14.85 – 68.72	10.83 – 77.41		
S.creat After 1 week	Mean ± SD	1.70 ± 0.45	1.63 ± 0.60	0.695•	0.489
	Range	1 – 3.5	0.8 – 5		
Creatinine clearnce after 1 week	Mean ± SD	47.18 ± 14.84	52.80 ± 16.68	-1.780•	0.078
	Range	16.98 – 96.32	13.11 – 91.26		

There was no significant difference between the basal serum creatinine in control group and Nicorandil group (1.61 ± 0.18 vs 1.65 ± 0.22, P=0.350) and baseline creatinine clearance between both groups (47.00 ± 8.70vs 48.65 ± 9.60, P=0.370), serum creatinine level 24 hours after the procedure (1.84 ± 0.34 vs 1.79 ± 0.31, P=0.464) and creatinine clearance between both groups 24 hours after prost procedure (42.47 ± 10.38 vs 45.78 ± 12.59, P=0.154), creatinine level 72 hours after the procedure (1.93 ± 0.54 vs 1.80 ± 0.76, P=0.335).

However, there was a significant difference among both groups as regards creatinine clearance 72 hours after the procedure (41.72 ± 12.16 vs 47.88 ± 14.74, P=0.025).

There was no significant difference between the serum creatinine in control group and Nicorandil group 1 week after the procedure (1.70 ± 0.45vs 1.63 ± 0.60, P=0.489) and creatinine clearance between both groups (47.18 ± 14.84 vs 52.80 ± 16.68, P=0.078).

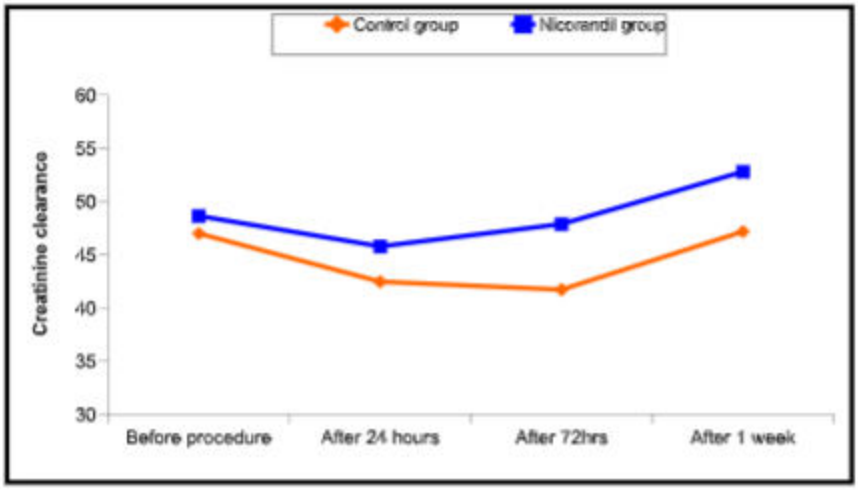

Figure (1): Comparison between control group and Nicorandil group as regards creatinine clearance measured 24 hours before, 24 hours after the procedure, 72 hours after the procedure and 1 week after the procedure.

Table (4): Comparison between both groups Nicorandil group and control group as regards contrast (type and amount), and the incidence of CIN.

		Control group	Nicorandil group	Test value	Sig.
		No. = 50	No. = 50		
Dye amount (ml)	Mean ± SD	137.40 ± 65.08	112.80 ± 67.52	1.855•	NS
	Range	50 – 400	50 – 500		
Dye type	Iso-osmolar	36 (72.0%)	40 (80.0%)	0.877*	NS
	Low-osmolar	14 (28.0%)	10 (20.0%)		
CIN	Yes	14 (28.0%)	6 (12.0%)	4.000*	S
	No	36 (72.0%)	44 (88.0%)		

No significant difference between the control group and Nicorandil group was demonstrated as regards dye amount (137.40 ± 65.08 vs 112.80 ± 67.52, P=0.067), and dye type (36 (72%) vs 40 (80%), P=0.349).

There was a significant difference as regards the rates of occurrence of CIN between both groups ,28% in control group and12% in the Nicorandil group.

Table (5): Comparison between non CIN group and CIN group associated risk factors as smoking status, family history of premature CAD, prior MI, prior angina, prior PCI, prior CABG, type I DM, type II DM, hypertension, dyslipidemia, PVD and CVS.

		No CIN No. = 80	CIN No. = 20	Test value	P-value
Smoking status	Yes	49 (61.2%)	8 (40.0%)	2.948*	0.086
	No	31 (38.8%)	12 (60.0%)		
Family history	Yes	26 (32.5%)	5 (25.0%)	0.421*	0.517
	No	54 (67.5%)	15 (75.0%)		
Prior MI	Yes	15 (18.8%)	6 (30.0%)	1.221*	0.269
	No	65 (81.2%)	14 (70.0%)		
Prior Angina	Yes	24 (30.0%)	8 (40.0%)	0.735*	0.391
	No	56 (70.0%)	12 (60.0%)		
Prior PCI	Yes	13 (16.2%)	6 (30.0%)	1.966*	0.161
	No	67 (83.8%)	14 (70.0%)		
Prior CABG	Yes	2 (2.5%)	0 (0.0%)	0.510*	0.475
	No	78 (97.5%)	20 (100.0%)		
Type I DM	Yes	1 (1.2%)	0 (0.0%)	0.253*	0.615
	No	79 (98.8%)	20 (100.0%)		
Type II DM	Yes	35 (43.8%)	14 (70.0%)	4.412*	0.036
	No	45 (56.2%)	6 (30.0%)		
Hypertension	Yes	55 (68.8%)	16 (80.0%)	0.983*	0.321
	No	25 (31.2%)	4 (20.0%)		
Dyslipidaemia	Yes	34 (42.5%)	10 (50.0%)	0.365*	0.546
	No	46 (57.5%)	10 (50.0%)		
PVD	Yes	2 (2.5%)	1 (5.0%)	0.344*	0.558
	No	78 (97.5%)	19 (95.0%)		
CVS	Yes	3 (3.8%)	1 (5.0%)	0.065*	0.799
	No	77 (96.2%)	19 (95.0%)		
	No	53 (66.2%)	12 (60.0%)		

No statistical difference was found between Non CIN group and CIN group as regards above mentioned risk factors except for DM. There was a significant difference between non CIN group and CIN group as regards type II DM (35 (43.8%) in CIN group vs 14 (70%), P=0.036) in CIN group.

Table (6): Comparison between non CIN group and CIN group as regards serum creatinine levels and creatinine clearance measured 24 hours before, 24 hours after the procedure, 72 hours after the procedure and 1 week after the procedure.

		No CIN No. = 80	CIN No. = 20	Test value	P-value	Sig.
Creat. before procedure	Mean ± SD	1.64 ± 0.20	1.61 ± 0.22	0.740•	0.461	NS
	Range	1.1 – 2.3	1.1 – 1.9			
Cr.clearance before procedure	Mean ± SD	48.64 ± 9.25	44.53 ± 8.12	1.818•	0.072	NS
	Range	12.46 – 74.44	29.58 – 57.39			
S.creat after 24 hours	Mean ± SD	1.73 ± 0.24	2.16 ± 0.39	-6.307•	0.000	HS
	Range	1.1 – 2.4	1.4 – 2.7			
Clearance 24 hrs after	Mean ± SD	46.83 ± 10.89	33.33 ± 7.39	5.239•	0.000	HS
	Range	11.33 – 74.44	19.44 – 46.18			
Cr.72hrs after	Mean ± SD	1.66 ± 0.25	2.66 ± 1.09	-7.483•	0.000	HS
	Range	1.1 – 2.3	1.4 – 6.5			
Clearance 72 hrs after	Mean ± SD	48.73 ± 11.89	29.10 ± 8.90	6.901•	0.000	HS
	Range	10.83 – 77.41	12.96 – 44.07			
S.creat After 1 week	Mean ± SD	1.52 ± 0.28	2.26 ± 0.82	-6.743•	0.000	HS
	Range	0.8 – 2.1	1.4 – 5			
Creatinine clearance after 1 week	Mean ± SD	54.09 ± 14.60	33.62 ± 9.43	5.956•	0.000	HS
	Range	13.11 – 96.32	14 – 44.99			

There was no significant difference between the non CIN and CIN groups as regards basal creatinine level (1.64 ± 0.20 vs 1.61 ± 0.22, P=0.461) and creatinine clearance (48.64 ± 9.25 vs 44.53 ± 8.12, P=0.072).

There was a significant difference between both groups as regards creatinine (1.73 ± 0.24 vs 2.16 ± 0.39, P=0.000) and clearance (46.83 ± 10.89 vs 33.33 ± 7.39, P=0.000) 24 hours after the procedure. There was, as well, a significant difference as regards the creatinine (1.66 ± 0.25 vs 2.66 ± 1.09, P=0.000) and clearance (48.73 ± 11.89 vs 29.10 ± 8.90, P=0.000) 72 hours after the procedure. There was, as well, a significant difference as regards the creatinine (1.52 ± 0.28 vs 2.26 ± 0.82, P=0.000) and clearance (54.09 ± 14.60 vs 33.62 ± 9.43, P=0.000) 1 week after the procedure. The values are obviously higher in the CIN group

The dye amount was highly significantly higher in the CIN group (108.88 ± 37.11 in non CIN vs 190.00 ± 110.50 in CIN group, P=0.000).

Discussion

CIN leads to increased morbidity, prolonged hospital stay and thereby, more health care costs. Today, the target is being focused on prevention. **(23)** The most frequent risk factor for of CIN is pre-existing CKD. **(23)** The incidence of CIN varies from 2% to 30%. Fortunately, most cases can be completely reversed within two to four weeks. **(25)**

The main finding of the current study is that in CKD patients, planned for cardiac catheterization in the setting of NSTACS, Nicorandil and adequate hydration is an effective and safe strategy for decreasing the incidence of CIN in comparison with hydration alone.

To our knowledge, there are five studies on the preventive role of Nicorandil in CIN. In 2016,Fan Y and his colleaguesconducted a study in China on the role of oral Nicorandil on CIN in CKD patients planned for elective cardiac catheterization. **(26)** In 2017, Leili Iranirad conducted a study in Iran about the role of Nicorandil treatment for prevention of CIN in high-risk patients who had at least two risk factors for CIN, planned for elective cardiac catheterization. **(27)** In 2016, Soo Hwan Park conducted a study in Korea on the preventive role of preprocedural administration of Nicorandil on the incidence of CIN in patients with AMI. **(28**) In 2013, a Korean study, titled the PRINCIPLE study, was carried out to assess the protective role of preprocedural intravenous treatment with Nicorandil in CKD patients, planned for CA. **(29)** Also, in 2016,Takahide Nawa's studyin Japan focused on the role of intravenous Nicorandil infusions 4 hours pre and 24 hours post CA on incidence of CIN in CKD patients, planned for CA. **(30)**

In the current study, we randomized 100 patients presented with NSTACS and their laboratory investigations revealed eGFR ≤60 mL/min/1.73m^2. Those patients were planned for CA and divided into two groups; A Nicorandil group (50 patients) who received standard prophylactic saline hydration in addition to Nicorandil 20 mg per day (10mg BID) 24 hours before and for 72 hours post the procedure and a control group (50 patients) who only received standard saline hydration.

In Fan Y study, 240 patients with eGFR of 60 mL/min/1.73m^2 or less, planned for elective cardiac catheterization, were randomly allocated into Nicorandil group (n = 120, 10 mg Nicorandil, three times daily from 2 days before to 3 days after procedure) and control group (n = 120, matching placebo as the same protocol).All patients were given an intravenous 0.9 % saline at a rate of 1 mL/kg/hr (0.5 mL/kg/hr for patients with LVEF <40 %) at least 6 hours pre and 12 hours post elective coronary procedure. **(26)**

In Leili Iranirad study, 128 patients with at least two risk factors for CIN planned for elective cardiac catheterization were randomly divided into Nicorandil group (n = 64, 10 mg Nicorandil, daily from half an hour before and up to 3 days after procedure and intravenous normal saline at rate of 1 mL/kg/hr, 2 hours before and 6 hours after the procedure) and control group (n = 64, just received intravenous hydration). **(27)**

In Takahide Nawa's study, 213 patients planned for elective PCI, with high serum cystatin C level, were randomly allocated into Nicorandil group (n = 106, 2 vials of Nicorandil (48 mg/vial) dissolved in 100 mL 0.9% saline, and dripped at rate of 0.1 mL/kg/hr, plus 0.9% saline hydration intravenously infused at 1.0 mL/kg/hr) and control group (n = 107,0.9% saline infusion only at 1mL/kg/hr, 4 hours before and 24 hours after the procedure). **(30)**

In the PRINCIPLE study, 166 patients were enrolled for elective CA, with an eGFR <60 mL/min/1.73m^2. In the Nicorandil group (n=81, 12 mg Nicorandil was dissolved in 100 mL of isotonic saline and given intravenously over half an hour just before CA). In the control group(n=85, 100 mL of 0.9% saline was administered by the same method). All patients were given intravenous infusion of hypotonic saline at a rate of 1 mL/kg/hr (for LVEF <40%) the rate was0.5 mL/kg/hr) at least 8 hours before and after an elective coronary procedure. **(29)**

In Soo Hwan Park study, a retrospective analysis between November 2005 and August 2011 was performed using clinical, laboratory and angiographic data of 1,492 AMI patients who performed PCI within 24 hours after symptom onset. The patients were allocated into two groups: Nicorandil group (n=442, 10 mg Nicorandil was administered orally twice a day prior to procedure) and control group (n= 1,050,not taking Nicorandil).

Post PCI in all patients, isotonic 0.9% saline was given intravenously at a rate of 1 mL/kg/hr (for LVEF <40%) the rate was0.5 mL/kg/hr) for 12 hours. **(28)**

In the current study, there was no statistical difference between Nicorandil group and control group as regards to the age (61.30 ± 8.73 years in Nicorandil group versus 64.16 ± 7.66 years in control group, P=0.085), gender (54% males in Nicorandil group versus 60% males in control group, , P= 0.545) , smoking status (62% in Nicorandil group versus 52% in control group, P= 0.313), hypertension (74% in Nicorandil group versus 68% in control group, P=0.437), Diabetes type II (48% in Nicorandil group versus 50% in control group, P=0.841) , PVD (6% in Nicorandil group versus 0% in control group, P=0.079), dyslipidemia(52% in Nicorandil group versus 36% in control group, P= 0.107), basal serum creatinine(1.65 ± 0.22 mg/dL in Nicorandil group versus 1.61 ± 0.18mg/dL in control group, P=0.350) and creatinine clearance (48.65 ± 9.60 in Nicorandil group versus 47.00 ± 8.70 in control group, P=0.370).

Similarly, there was no significant difference in the study by Fan Y as regards to the age (66.07 ± 6.37 in Nicorandil group versus 67.37 ± 6.33 in control group, P= 0.114), gender(88% males in Nicorandil group versus 95% in control group, P= 0.326), smoking status (71% in Nicorandil group versus 77% in control group, P= 0.507), hypertension(57.5 % in Nicorandil group versus 61.67 % in control group, P=0.598), type II DM(55% in Nicorandil group versus 51% in control group, P= 0.698) and basal serum creatinine(123.55 ± 10.77µmol/L in Nicorandil group versus 122.99 ± 10.39µmol/L in the control group, P=0.682). **(26)**

Also there was no significant difference in the study by Leili Iranirad as regards to the age (61.35 ± 11.77 in Nicorandil group versus 57.64 ± 12.42 in control group, P= 0.085), gender (60.9%% males in Nicorandil group versus 62.5%in control group, P= 0.856), smoking status (36.7% in Nicorandil group versus 31% in control group, P= 0.550), hypertension (54.7% in Nicorandil group versus 64.1% in control group, P=0.280), type II DM(42.2% in Nicorandil group versus 40.6% in control group, P= 0.858), basal serum creatinine 1.0859 ± 0.22 mg/dL in Nicorandil group versus 1.0359 ± 0.15 mg/dL in the control group, P=0.088) and creatinine clearance (76.39 ± 24.6 in Nicorandil group versus 83 ± 28.1in control group, P=0.067). **(27)**

Similarly ,in the PRINCIPLE study**,** there was no significant difference as regards to the age (70.8±9.6 in Nicorandil group versus 69.1±10.3 in control group, P= 0.291), gender (72.6% in Nicorandil group versus 67.1% in control group, P= 0.581), smoking status (23.3% in Nicorandil group versus 23.7% in control group, P= 0.892), Hypertension(78.1% in Nicorandil group versus 80.3% in control group, P= 0.900), type II DM(41.1% in Nicorandil group versus 55.3% in control group, P= 0.117) and creatinine

clearance(37.5±13.4in Nicorandil group versus 40.1±13.9in control group, P= 0.248). **(29)**

The best global index of renal function is GFR. In elderly, Serum creatinine is not affected by significant decline in GFR. Any considerable decrease in muscle bulk with aging, diet and medications may affect it. **(31)** Creatinine clearance provides a reasonably reliable indicator of GFR. **(32)** Therefore, The United States National Kidney Foundation recommends using eGFR calculated from the serum creatinine as an indicator of renal function rather than using serum creatinine alone. **(33)**

In the current study, creatinine clearance after 72 hours post procedure was significantly higher in Nicorandil group (47.88 ± 14.74 mL/min/1.73 $m^{2)}$ than control group (41.72 ± 12.16 mL/min/1.73 $m^{2)}$, P=0.025.This agrees with the findings of Fan Y study where eGFR after 48 hours of the procedure was significantly higher in the Nicorandil group, compared to the control group (eGFR = 43.29 ± 6.88 mL/min/1.73 m^2 in Nicorandil group versus 40.27 ± 7.45 mL/min/1.73 m^2 in control group, P=0.001) **(26)**.

Also, inLeili Iranirad study, there were significant differences between the two groups in serum creatinine and eGFR 72 hours after CM exposure ($p < 0.05$) **(27).**

In contrast, the PRINCIPLE study showed no significant difference between the two groups regarding the serum creatinine 48 hours post procedure (1.72±0.78 in Nicorandil group versus 1.63±0.57 in control group, P= 0.469). **(Ko YG et al., 2013)**Also, in the study by Soo Hwan Park, the relative changes in serum creatinine from baseline to maximal creatinine level within 48 hours were not significantly different between the Nicorandil and control groups. **(28)**

Regarding the dye used in the current study, both iso-osmolar and low-osmolar types were used with no statistical difference between both groups (P=0.349). The dye amount was 112.80 ± 67.52ml in the Nicorandil group and 137.40 ± 65.08 ml in the control group (P=0.067), with no significant variation in the dye amount between both groups. This agrees with data provided by Fan Y (145.3 ± 51.6 in Nicorandil group versus 149.2 ± 57.0 in control group, P= 0.579) **(26)**, thePRINCIPLE study (125.6±69.1 in Nicorandil group versus 126.9±74.6 in control group, P= 0.916) **(29)** and Takahide Nawa's study (135.2 ± 57.0 in Nicorandil group versus 146.3 ± 63 in control group, P= 0.206). **(30)**

In the current study, there was a significant difference regarding the rate of CIN occurrence among Nicorandil (12%) versus control group (28%), with P value =0.046.

This coincides with Fan Y study (6.67% in Nicorandil group versus 17.5% in control group, P= 0.017) **(26)**, Takahide Nawa study (2% in Nicorandil group versus

10.7% in control group, P= 0.033) (**30**) and Leili Iranirad study (4.7% in Nicorandil group versus 21.9% in control group, P= 0.008). **(27)**

In contrast, in the PRINCIPLE study, the rate of CIN occurrence was not significantly different between the Nicorandil group (6.8%) and control group (6.6%), P= 0.794. **(29)** Also in Soo Hwan Park, no significant difference was found between Nicorandil group (25.1%) and control group (27.3%), P= 0.405. **(28)**

In the current study, another comparison was made between patients with CIN (n=20) and those without CIN (n=80). There was no statistical difference between the CIN and no CIN groups as regards to the age and sex, although female gender and aging are considered as independent predictors of CIN. **(34)(35).**

In the current study, a significant difference was demonstrated between the CIN and no CIN groups as regards to the prevalence of DM type II (70% in CIN group versus 34% in no CIN group, P=0.036). Many studies have pointed that diabetes is a predictor of CIN and it remains significant as an independent predictor in most, but not all, multivariate analysis. **(34)** This agrees with Soo Hwan Park study (P =0.001) **(28)** and in contrast to Takahide Nawa study (43.8% in CIN group versus 54.3% in no CIN group, P=0.43) (**30)** andFan Y study (P=0.441). **(26)**

The other factor that appeared significantly higher in the CIN group is the dye amount (190.00 ± 110.50 ml in CIN group versus 108.88 ± 37.11 ml in no CIN group, P=0.000). This agrees with Fan Y study, where the results of multiple logistic regression analysis showed that CM volume ≥150 mL (OR = 5.996, 95 % CI = 2.307–15.169, P = 0.001) was independentpredictor of CIN after procedure within 72 hours. **(26)** In contrast, Takahide Nawa study showed no significant difference between both groups, where 43.8% of CIN group used CM more than 140 ml versus 49.4% of no CIN group, p=0.19). (**30**)Therefore, currently, periprocedural intravenous hydration, using iso-osmolar and/or low-osmolar CM instead of high-osmolar agents and limiting the dosage of CM are the confirmed strategies against CIN **(36) (37)**

Multiple studies have shown that an increased volume of CM is correlated with the occurrence of CIN. **(38) (39)** Mehran et al. presented a simplified risk score for assumption of CIN after PCI. **(40)** Mehran study revealed that every 100 mL of CM could be raised one point in the Mehran contrast nephropathy risk score. Rihal et al study also revealed that each 100 ml increase in the contrast volume was accompanied by a 12% rise in the risk of CIN. **(41)**

The current study was limited by performed in a single center, with a relatively small sample size,100 patients, which could have attenuated the statistical power of the conclusions. Yet, statistical significance in the current study was achieved despite the

small sample size. Still, more future studies are needed to further assess the results of the current study.

The current study recommend that all patients exposed to CM should be evaluated for their risk of CIN. All patients exposed to any CM before any procedure should be well hydrated. Adequate saline hydration is recommended 12 hours before CA procedures and is considered the main approved measure for the prevention of CIN. Follow-up serum creatinine should be obtained at not less than 24 h or more than 72 h following CM administration. Medications that have an adverse effect on renal function should be stopped before and after CM exposure. The volume of CM administered, particularly to high-risk patients, should be the least amount needed for diagnosis and intervention and preferable to be low or iso-osmolar CM.

Conclusion

In the current study, the main finding is that in patients with renal impairment, undergoing cardiac catheterization in the setting NSTACS, Nicorandil and adequate hydration is an effective and safe strategy for decreasing the occurrence of CIN in comparison with hydration only. Both DM and increased volume of CM are predictors of CIN occurrence.

List of abbreviations

- PCI…percutaneous coronary intervention
- CA…. CA.
- CIN…. Contrast induced nephropathy.
- CKD…chronic kidney disease.
- ATP…Adenosine Triphosphate-sensitive.
- CM…. CM.
- NSTACS…non ST elevation acute coronary syndrome.
- NSTEMI…non ST elevation acute myocardial infarction.
- CCBs…Calcium channel blockers.
- ACS… acute coronary syndrome.

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