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Original Article

Prevention of contrast induced nephropathy by ischemic preconditioning in patients undergoing percutaneous coronary angiography

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ABSTRACT

Background: Contrast-induced nephropathy (CIN) is the acute deterioration of renal function after parenteral administration of radio contrast media in the absence of other causes. The true incidence of CIN varies because of differences among the published studies in the definition of CIN, the proportion of high-risk patients, the types of contrast media, and the use of preventive measures. Remote ischemic preconditioning (IPC) may offer a non-pharmacological prevention strategy for lowering CIN in patients undergoing coronary procedures. The assumption that IPC produces protective effects on tissues or organs by multiple brief cycles of ischemia and reperfusion applied to another remote tissue or organ.
Aim: To investigate the effect of ischemic preconditioning in prevention of CIN in patients with renal impairment undergoing percutaneous coronary angiography.
Results: In this study, 100 patients undergoing elective PCI with a base line creatinine clearance <60 ml/min were studied. Patients were divided into two equal groups (ischemic preconditioning group and control group). The incidence of CIN was markedly lower in ischemic preconditioning group 14% VS 38% in control group. The incidence of CIN difference as was found to be (24%). Amount of dye used, decreased LVEF and presence of a significant LAD lesion were significant risk factors for occurrence of CIN.
Conclusions: The current study showed that remote ischemic preconditioning plays an important role in prevention of CIN in patients undergoing PCI with renal impairment GFR < 60 ml/min. The amount of contrast, decreased LVEF, and presence of LAD significant lesion were significant risk factors for developing of CIN and these subgroups benefited from application of ischemic preconditioning.

1. Introduction

Contrast induced nephropathy (CIN) is a complication of coronary procedures, and is associated with unfavorable outcomes, including major cardiovascular events, prolonged hospitalization, and even early death in certain individuals.[1,2]

Chronic kidney disease (CKD) is an important risk factor for the incidence of CIN.[3] Pre-existing renal dysfunction with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m ^{2} is the one of the most important predictors of contrast induced acute kidney injury (CI-AKI), and its level correlates positively with the incidence of CI-AKI.[3,4] Other risk factors include diabetes mellitus, hypovolemia, administration of large amounts of contrast medium, and use of drugs that interfere with the regulation of renal perfusion.[4]

Remote ischemic preconditioning can offer a non-pharmacological mechanisms aiming at decreasing the incidence of CIN in patients undergoing coronary interventions. It is postulated that ischemic preconditioning promotes protective effects on tissues or organs by multiple brief cycles of ischemia and reperfusion applied to another remote tissue or organ.[5–7]

The role of ischemic preconditioning to reduce the incidence of CI-AKI is not fully understood. In our prospective, randomized, sham-controlled study we hypothesized that ischemic preconditioning applied prior to coronary interventional procedures may be beneficial in the prevention of CIN in patients at high risk.

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1.1. Aim of the work

To investigate the effect of ischemic preconditioning in the prevention of contrast induced nephropathy in patients with renal impairment undergoing percutaneous coronary angiography.

2. Patients and methods

One hundred patients with a calculated GFR of <60 ml/min/1.73 m^2 were included. They were patients presenting to the Cardiology department of Ain Shams University Hospitals to undergo elective percutaneous coronary intervention, from the period from April 2015 till October 2015.

One type of radio-contrast dye was used which was non-ionic, low-osmolar dye (ULTRAVIST®, Bayer Healthcare). The amount of the radio-contrast medium given was calculated in every case.

2.1. Exclusion criteria

1. Recent exposure to radiographic contrast.
2. Known allergy to radiographic contrast.
3. Chronic peritoneal or hemodialysis treatment.

These included patients were consecutively divided through 1:1 randomization into 2 groups after screening for eligibility criteria regardless of the base line serum creatinine:

Group 1: which consisted of 50 patients who will had PCI with ischemic preconditioning. with a proper hydration with 0.9% sodium chloride as infusion of 3 ml/kg for 1 h prior the procedure followed by an infusion of 1 ml/kg/h for 6 h after the procedure.

Group 2: which consisted of 50 patients who had PCI without ischemic preconditioning. with a proper hydration with 0.9% sodium chloride as infusion of 3 ml/kg for 1 h prior the procedure followed by an infusion of 1 ml/kg/h for 6 h after the procedure.

3. Methods

Patients were subjected to the following:

1. Proper history taking including:
   (a) Age & gender of the patient (for the purpose of calculation of the serum creatinine clearance by applying the Cockcroft-Gault formula (Estimated creatinine clearance equals {((140-age in years) × weight in kg)/(72 × serum creatinine in mg/dl)}. The result was multiplied by 0.8 in females.[8]
   (b) Associated risk factors such as diabetes mellitus, hypertension, dyslipidemia and smoking.
   (c) History of allergy to radiographic contrast.
2. Clinical examination:
   (a) General examination: including weight and height of patients.
   (b) Local cardiac examination.
3. Samples were withdrawn for measurement of serum creatinine prior to the procedure and 48 h after the procedure, whether inpatient or out-patient. Patients was considered to have contrast induced nephropathy if there was an absolute increase in serum creatinine levels by ≥0.5 mg/dL or a relative increase in serum creatinine by ≥25% from baseline, or a creatinine clearance decrease more than 50% over the baseline value (RIFLE classification).[9]
4. 4 A nonionic contrast agent used during the procedure.
5. Patients in group 1 had ischemic preconditioning by performing four cycles of alternating 5-min inflation and 5-min deflation of a standard upper-arm blood-pressure cuff to individuals' systolic blood pressure plus 50 mmHg to induce transient and repetitive arm ischemia and reperfusion. This was done in the waiting ward before the procedure while being hydrated, thus not causing delay. The time between last inflation cycle and CA start was less than 45 min.
6. Group 2 underwent coronary angiography, and had an upper arm blood pressure cuff placed but without ischemic preconditioning as a sham procedure.

3.1. Data management and analysis

Statistical analyses were performed by using SPSS system for Windows (version 20 Chicago, IL, USA), Continuous variables were presented as mean ± SD and categorical variables were expressed as percentages. Wilcoxon signed ranks test for comparing between results before and after PCI. The receiver operational characteristic (ROC) analyses was performed and best cut off value was determined and at that point sensitivity and specificity were determined, the results were considered significant when the p value was less than .05 (see Tables 1–4).

4. Results

Regarding creatinine at baseline, at follow up and percent of change, there was no significant difference between the both groups in baseline creatinine, but there was a significant difference in follow up creatinine p = (.013) in group 2 and highly significant difference in percentage of change p = (.007).

When looking at the occurrence of CIN, 7 patients of 50 with ischemic preconditioning (14%) developed CIN, while 19 patients in control group (38%) developed CIN with highly significant difference between both groups p = (.006).

Table 5 shows that, after adjustment to all factors it was shown that amount of contrast, LVEF, Significant LAD and absence of preconditioning were independent factors for the occurrence CIN.

5. Discussion

Contrast induced nephropathy is not an infrequent complication following coronary diagnostic and interventional procedures. Moreover, it has been proven to be an independent predictor of one-year mortality in patients with ischemic heart disease. The incidence of contrast induced nephropathy varies substantially among several studies due to the lack of a uniform definition.[10] Rates of contrast induced nephropathy may occur in 50% of patients, depending on the presence of risk factors, such as chronic renal insufficiency and heart failure or diabetes mellitus.[1]

The exact mechanism of contrast nephropathy is not entirely comprehended and it may relate to alteration in renal hemodynamics, direct toxic effects on tubular renal epithelial cells, and damage by oxygen radicals.[11] The most common mechanism of CI-AKI is the induction of renal ischemia, possibly due to the iodinated contrast medium-induced reduction in renal blood flow as well as a surge in the oxygen free radical mediated direct tubular toxicity.[12] The underlying mechanism for pathological changes in CI-AKI consists of the contrast medium-induced natriuresis and diuresis, which activates the tubulu-glomerular feedback response with resultant vasoconstriction of the glomerular afferent arterioles producing a decrease in GFR.

There are limited effective prophylactic medications to prevent CI-AKI. Dopamine, mannitol, aminophylline, fenoldopam, captopril, furosemide, atrial natriuretic peptide, calcium channel block-

Table 1
Comparison between group 1 and 2 subjects regarding their demographic and clinical data.

		Pre-conditioning				P
		Yes		No		
		Mean	±SD	Mean	±SD	
Age		65.16	7.98	65.1	7.07	1.0[a]
BMI		29.80	4.06	29.26	3.83	.500[a]
Amount of contrast		125.20	37.59	119.80	38.41	.479[a]
Sex	Male (n%)	29	58.0%	29	58.0%	1.0[b]
	Female (n%)	21	42.0%	21	42.0%	
Smoking	Yes (n%)	28	56.0%	26	52.0%	.688[b]
	No (n%)	22	44.0%	24	48.0%	
HTN	Yes (n%)	32	64.0%	34	68.0%	.673[b]
	No (n%)	18	36.0%	16	32.0%	
DM	Yes (n%)	33	66.0%	33	66.0%	1.0[b]
	No (n%)	17	34.0%	17	34.0%	
Dyslipidemia	Yes (n%)	21	42.0%	18	36.0%	.539[b]
	No (n%)	29	58.0%	32	64.0%	
Family history of CAD	Yes (n%)	23	46.0%	21	42.0%	.687[b]
	No (n%)	27	54.0%	29	58.0%	
ACEI usage		36	72.0%	37	74.0%	.786[b]
SU usage		20	40.0%	19	38.0%	.854[b]
SBP (mmHg)		138.0	13.44	139.30	12.12	.613[a]
DBP (mmHg)		83.60	9.85	82.80	10.11	.689[a]
HR (beats/minute)		74.14	10.43	73.96	10.47	.932[a]
LVEF (%)		53.84	6.57	53.34	6.57	.704[a]

BMI = Body mass index.
HTN = Hypertension.
DM = Diabetes mellitus.
CAD + Coronary artery disease.
ACEI = Angiotensin Converting Enzyme Inhibitor.
SU = Sulphonylurea.
SBP = Systolic blood pressure.
DBP = Diastolic blood pressure.
HR = Heart rate.
LVEF = Left ventricular ejection fraction.
[a] Student *t* test.
[b] Chi-square tests.

Table 2
Comparison between group 1 and 2 regarding significantly affected coronary arteries.

	Pre-conditioning				P
	Yes		No		
	N	%	N	%	
Significant Left main affection	0	0	0	0.0	–
Significant LAD affection	37	74.0	31	62.0	.198[a]
Significant LCX affection	11	22.0	15	30.0	.699[a]
Significant RCA affection	18	36.0	15	30.0	.523[a]

[a] Chi-square tests.

ers and alprostadil were not effective in reducing the incidence of CI-AKI.[13] The first studies studying the ability of the N-acetyl cysteine (NAC) to prevent CI-AKI were promising. However, the role of NAC in prevention of CI-AKI has been questioned when subsequent larger trials failed to demonstrate a benefit.[14]

The theory that remote organs release factors such as adenosine or bradykinin into the circulation, which subsequently protects the remote organ. Other postulated mechanisms may include erythropoietin, activation of the K^+ ATP channel, delta 1-opioid, nitric oxide, and free radicals. Some studies have suggested that the protective effect of remote ischemic preconditioning may be due to the anti-inflammatory or anti-oxidant effects, thus decreasing extracellular levels of injurious metabolites, such as protons and lactate. Additionally, some other studies also have postulated a neurogenic pathway.[15]

In our study, 100 patients undergoing PCI with baseline creatinine clearance <60 mg/dl were studied. Patients were divided into 2 groups (ischemic preconditioning group and control group), 50 patients in each group. The incidence of CIN was markedly

Table 3
Comparison between group 1 and 2 as regards creatinine, and creatinine clearance at baseline, at follow up and percent of change.

	Pre-conditioning						P
	Yes			No			
	Mean	±SD	Median	Mean	±SD	Median	
Baseline creatinine (mg/dl)	1.68	0.13	1.7	1.69	0.12	1.7	.814[a]
FUP Creatinine (mg/dl)	1.90	0.26	1.8	2.06	0.36	2.0	.013[a]
% Change in creatinine	12.89	13.01	11.1	21.42	16.05	12.5	.007[b]
Creatinine clearance at baseline	45.81	7.89	45.0	44.60	7.72	44.5	.439[a]
Creatinine clearance at FU	41.17	8.52	41.5	37.57	9.02	36.3	.043[a]
% Change in creatinine clearance	10.33	9.73	10.0	16.25	10.64	11.2	.009[b]

[a] Student *t* test.
[b] Mann Whitney test.

Table 4
Comparison between group 1 and 2 as regards occurrence of CIN.

		Pre-conditioning				P
		Yes		No		
		No.	%	No.	%	
CIN	Yes	7	14.0	19	38.0	.006[a]
	No	43	86.0	31	62.0	

[a] Chi-square tests.

Table 5
Multivariate regression to study independent factors affecting occurrence of CIN.

	OR[a]	P	95.0% CI for OR[b]	
Age	1.115	.132	0.968	1.284
BMI	0.757	.140	0.523	1.096
Male	1.915	.576	0.196	18.694
HTN	1.407	.776	0.134	14.720
Smoking	5.986	.270	0.249	144.174
DM	6.520	.143	0.531	80.101
Dyslipidemia	0.343	.480	0.018	6.673
Positive family history of CAD	0.690	.789	0.045	10.533
Amount of contrast	1.031	.048	1.000	1.062
SBP	0.942	.346	0.832	1.066
DBP	1.106	.321	0.907	1.348
HR	1.090	.165	0.965	1.231
LVEF	0.814	.034	0.673	0.984
Significant LAD	32.627	.041	1.157	920.235
Significant LCX	0.010	.060	0.000	1.214
Significant OM	0.477	.729	0.007	31.068
Significant RCA	2.531	.617	0.066	96.722
Baseline creatinine	0.338	.805	0.000	1872.892
No preconditioning	125.41	.002	5.824	2700.642

[a] Odds ratio.
[b] Confidence interval.

lower in ischemic preconditioning group 14% and 38% in control group.

We measured the effect of remote ischemic preconditioning, induced by intermittent upper arm ischemia prior to invasive coronary procedure, which dramatically reduced the incidence of contrast medium-induced nephropathy in patients with chronic kidney disease.

In our study, the amount of contrast was an important risk factor in the occurrence of CIN (P = .001). The volume of contrast medium administered during coronary angiography correlated with an increased risk of CIN. In a previous study of more than 7000 patients, the use of 100 ml of contrast medium administered was correlated with a hazard ratio for CIN of 1.12.[1] Another study limited including patients with preexisting renal disease revealed a ten-fold risk of CIN when more than 125 ml of contrast medium was given.[16] Rather than using an absolute threshold, investigators showed that exceeding a patient-specific volume (based on body weight and serum creatinine concentration) was associated with a 12-fold increased risk for hemodialysis.[17]

Left ventricular ejection fraction was similarly found to be a predictor of occurrence of contrast induced nephropathy (P = .0001). Patients with congestive heart failure were more susceptible to occurrence of CIN. Reduced left ventricular ejection fraction, congestive heart failure class III or IV, or even a history of congestive heart failure are all independent risk factors for CIN and entail even greater risk in patients with diabetes mellitus or renal disease. The risk associated with congestive heart failure is likely due to abnormalities in renal blood flow due to low cardiac output.[1]

Presence of significant LAD disease also showed a significant relationship to the occurrence of CIN (p = .001) which can be attributed to the territory supplied by LAD and its sharing in the left ventricular ejection fraction, with no other studies addressing this point.

Ischemic preconditioning was performed to patients of Group 1 (50 patients) whereas patients in group 2 received only hydration. Only 14% of the patients with ischemic preconditioning developed CIN. While, 38% of the patients who were not randomized to ischemic preconditioning developed CIN. This difference was statistically significant ($P = .06$). On the other hand, CIN was much higher in group 2 patients despite administering adequate hydration confirming that ischemic preconditioning is a potential protective measure to decrease the incidence of CIN in patients undergoing PCI.

Similarly, **Er et al.**, in RENO-PRO trial found that contrast media induced nephropathy, occurred in (12%) in the remote preconditioning group versus (40%) in the control group the incidence of CIN in patients with P = .002.[7]

In 2014 a meta-analysis of 11 randomized Trials about remote ischemic preconditioning in reduction of perioperative cardiac and renal Events in patients undergoing elective coronary intervention **Pei et al.**, showed that remote ischemic preconditioning significantly reduced perioperative incidence of contrast induced nephropathy (p = .04) and it may offer cardiorenal protection by reducing the incidence of MI and AKI in patients undergoing elective PCI.[18] Another meta-analysis showed the periprocedural benefit of RIPC whether in coronary angioplasty or even in cardiac surgery.[19]

To conclude, the current study proved that RIPC plays a role in the prevention of CIN in patients undergoing PCI with underlying renal impairment (GFR < 60 mg/dl). The amount of contrast, decreased LVEF, and presence of LAD significant lesion were significant risk factors for developing of CIN and these subgroups benefited from application of ischemic preconditioning.

6. Summary and conclusion

Contrast-induced nephropathy (CIN) is the deterioration of renal function after parenteral administration of contrast media in the absence of other causes. The exact incidence of CIN is difficult to assess accurately because of differences among the various published studies in the definition of CIN, the proportion of high-risk patients, the types of contrast media, and the use of preventive measures.

In this study, 100 patients undergoing PCI with base line creatinine clearance <60 mg/dl were studied. Patients were divided into 2 groups (ischemic preconditioning group and control group), 50 patients in each group. The incidence of CIN was markedly lower in ischemic preconditioning group 14% VS 38% in control group.

The incidence of CIN difference as was found to be (24%). amount of dye used, decreased LVEF and presence of significant LAD lesion was significant risk factors for occurrence of CIN.

Conflict of interest

The authors declared that there is no conflict of interest.

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