Original Article

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

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A R T I C L E   I N F O

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A B S T R A C T

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 m² 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.5

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.6,7

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 m² 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 \((140 \text{- age in years}) \times \text{weight in kg})/(72 \times \text{serum creatinine in mg/dl})\). 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. 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 PCI 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 tubulo-glomerular feedback response with resultant vasoconstriction of the glomerular afferent arteri-oles producing a decrease in GFR.

There are limited effective prophylactic medications to prevent CI-AKI. Dopamine, mannitol, aminophylline, fentanyl, captopril, furosemide, atrial natriuretic peptide, calcium channel block-
ers and alprostadil were not effective in reducing the incidence of CI-AKI. 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. 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.

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 1 | Comparison between group 1 and 2 subjects regarding their demographic and clinical data. |
|---------|---------------------------------|
|         | Pre-conditioning | P |
|         | Yes | Mean ±SD | No | Mean ±SD |
| Age     | 65.16 | 7.98 | 65.1 | 7.07 | 1.0 | 500 |
| BMI     | 29.80 | 4.06 | 29.26 | 3.83 | .500 |
| Amount of contrast | 12.20 | 37.59 | 119.80 | 38.41 | .479 |
| Sex     | Male (n%) | 29 | 58.0% | 29 | 58.0% | 1.0 |
| Smoking | Female (n%) | 21 | 42.0% | 21 | 42.0% |
| HTN     | Yes (n%) | 28 | 56.0% | 26 | 52.0% | .688 |
| DM      | No (n%)  | 22 | 44.0% | 24 | 48.0% |
| Dyslipidemia | Yes (n%) | 32 | 64.0% | 34 | 68.0% | .673 |
| Family history of CAD | No (n%)  | 18 | 36.0% | 16 | 32.0% |
| ACEI usage | 36 | 72.0% | 37 | 74.0% | .786 |
| SU usage | 20 | 40.0% | 19 | 38.0% | .854 |
| SBP (mmHg) | 138.0 | 13.44 | 139.30 | 12.12 | .613 |
| DBP (mmHg) | 83.60 | 9.85 | 82.80 | 10.11 | .689 |
| HR (beats/minute) | 74.14 | 10.43 | 73.96 | 10.47 | .932 |
| LVEF (%) | 53.84 | 6.57 | 53.34 | 6.57 | .704 |

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.  

| Table 2 | Comparison between group 1 and 2 regarding significantly affected coronary arteries. |
|---------|---------------------------------|
|         | Pre-conditioning | P |
|         | Yes | % | No | % |
| Significant Left main affection | 0 | 0 | 0 | 0 | .198 |
| Significant LAD affection | 37 | 74.0 | 31 | 62.0 | .198 |
| Significant LCX affection | 11 | 22.0 | 15 | 30.0 | .699 |
| Significant RCA affection | 18 | 36.0 | 15 | 30.0 | .523 |

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 | Mean ±SD | Median | No | Mean ±SD | Median |
| Baseline creatinine (mg/dl) | 1.68 | 0.13 | 1.7 | 1.69 | 0.12 | 1.7 | .814 |
| FUP Creatinine (mg/dl) | 1.90 | 0.26 | 1.8 | 2.06 | 0.36 | 2.0 | .013 |
| % Change in creatinine | 12.89 | 13.01 | 11.1 | 21.42 | 16.05 | 12.5 | .007 |
| Creatinine clearance at baseline | 45.81 | 7.89 | 45.0 | 44.60 | 7.72 | 44.5 | .439 |
| Creatinine clearance at FUP | 41.17 | 8.52 | 41.5 | 37.57 | 9.02 | 36.3 | .043 |
| % Change in creatinine clearance | 10.33 | 9.73 | 10.0 | 16.25 | 10.64 | 11.2 | .005 |

| a | Student t test.  
| b | Mann Whitney test.  

NAC in prevention of CI-AKI has been questioned when subsequent larger trials failed to demonstrate a benefit. 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.

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
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. 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 used.22

Identifying patients, the types of contrast media, and the use of preventive measures.

In this 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 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 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.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Rihal CS, Textor SC, Grill DE, et al.. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2000;105:2259–2264. https://doi.org/10.1161/01.CIR.0000016043.87291.33
2. Best PJM, Lennon R, Ting HH, et al.. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2002;39:1113–1119. https://doi.org/10.1016/S0735-1097(02)01745-X
3. Gruberg L, Mintz GS, Mehran R, Sangagias I, Lansky AJ, Kent KM, et al.. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol. 2000;36:1542–1548.
4. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, et al. Risk prediction of contrast-induced nephropathy. *Am J Cardiol*. 2006;98:27K–36K. https://doi.org/10.1016/j.amjcard.2006.01.022.

5. Ali ZA, Callaghan CJ, Lim E, Ali AA, Nouraei SA, Akthar AM, et al. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation*. 2007;116 (Suppl):I98–I105. https://doi.org/10.1161/circulationaha.106.679167.

6. Chen Y, Zheng H, Wang X, Zhou Z, Luo A, Tian Y. Remote ischemic preconditioning fails to improve early renal function of patients undergoing living-donor renal transplantation: a randomized controlled trial. *Transplantation*. 2013;95:e4–e6. https://doi.org/10.1097/TP.0b013e3182782f5a.

7. Er F, Nia AM, Dopp H, et al. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). *Circulation*. 2012;126:296–303. https://doi.org/10.1161/CIRCULATIONAHA.111.003670.

8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.

9. Lopes José António, Jorge Sofia. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J*. 2013;6:8–14. https://doi.org/10.1093/ckj/sct016.

10. Sudarsky D, Nikolsky E. Contrast-induced nephropathy in interventional cardiology. *Int J Nephrol Renovasc Dis*. 2011;4:85–99.

11. Brezis M, Rosen S. Hypoxia of the renal medulla: implications for diseases. *N Engl J Med*. 1995;332:647–655.

12. Katholi RE, Woods Jr WT, Taylor GJ, Deitrick CL, Womack KA, Katholi CR, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis*. 1998;32:64–71. https://doi.org/10.1053/ajkd.1998.v32.pm9669426.

13. Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA*. 2003;290:2284–2291. https://doi.org/10.1001/jama.290.17.2284.

14. Webb JC, Pate GE, Humphries KH, Buller CE, Shalansky S, Al Shamari A, et al. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast induced nephropathy after cardiac catheterization: lack of effect. *Am Heart J.* 2004;148:422–429. https://doi.org/10.1016/j.ahj.2004.03.041.

15. Lang SC, Elsasser A, Scheler C, Vetter S, Tiefenbacher CP, Kubler W, et al. Myocardial preconditioning and remote renal preconditioning: identifying a protective factor using proteomic methods? *Basic Res Cardiol*. 2006;101:149–158. https://doi.org/10.1007/s00395-005-0565-0.

16. Taliercio CP, Vlietstra RE, Fisher LD, Burnett JC. Risks for renal dysfunction with cardiac angiography. *Ann Intern Med*. 1986;104:501–504. https://doi.org/10.7326/0003-4819-104-4-501.

17. Freeman RV, O’Donnell M, Share D. Blue Cross-Blue Shield of Michigan Cardiovascular Consortium (BMC2). Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol*. 2002;90:1068–1073.

18. Pei H, Wu Y, Wei Y, Yang Y, Teng S, et al. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. *PLoS ONE*. 2014;9:e115500. https://doi.org/10.1371/journal.pone.0115500.

19. Jiachang Hu, Liu Shaopeng, Jia Ping, et al. Protection of remote ischemic preconditioning against acute kidney injury: a systematic review and meta-analysis. *Critical Care*. 2016;20:111. https://doi.org/10.1186/s13054-016-1272.