The Egyptian Heart Journal (2015) 67, 315–323

HOSTED BY

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Egyptian Society of Cardiology

The Egyptian Heart Journal

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ORIGINAL ARTICLE

Cardio- and reno-protective effect of remote ischemic preconditioning in patients undergoing percutaneous coronary intervention. A prospective, non-randomized controlled trial

Ayman K.M. Hassan [a,*], **Hamdy Shams-Eddin** [a], **Mona H.M. Abdel-Rahim** [b], **Heba A. Abd El-Hafeez** [c], **Sadat Edroos** [d]

[a] *Department of Cardiology, Faculty of Medicine, Assiut University, Egypt*
[b] *Department of Microbiology and Immunology, Faculty of Medicine, Assiut University, Egypt*
[c] *Department of Clinical Pathology, Faculty of Medicine, Assiut University, Egypt*
[d] *Department of Cardiology, Princess Alexandra Hospital, Harlow, Essex, United Kingdom*

Received 19 June 2015; accepted 16 August 2015
Available online 7 September 2015

KEYWORDS

Remote ischemic preconditioning;
Elective percutaneous coronary intervention;
Contrast induced nephropathy;
PCI-related myocardial infarction

Abstract *Objectives:* This study assessed the cardio- and renoprotective effect of remote ischemic Preconditioning (PreC) in patients undergoing percutaneous coronary intervention (PCI).
Background: Myocyte necrosis and contrast induced nephropathy (CIN) occur frequently in PCI and are associated with subsequent cardiovascular events. Methods: Two hundred consecutive patients undergoing elective PCI with normal baseline troponin-I (cTnI) values were recruited. Subjects were systematically allocated into 2 groups: 100 patients received PreC (created by three 5 min inflations of a blood pressure cuff to 200 mmHg around the upper arm, separated by 5 min intervals of reperfusion) <2 h before the PCI procedure, and control group ($n = 100$).
Results: The incidence of PCI-related myocardial infarction (MI 4a) at 24 h after PCI was lower in the PreC group compared with control group (41% vs 64%, $P = 0.02$). Subjects who received PreC had significant trend toward lower incidence of CIN at 72 h after contrast exposure (4 vs. 11, $P = 0.05$) and less chest pain during stent implantation compared to control group. At 3 months, the major adverse event rate was lower in the PreC group (6 vs. 14 events; $P = 0.04$).
Conclusions: The use of PreC < 2 h before PCI, reduces the incidence of PCI-related MI 4a, tends to decrease the incidence of CIN and improves ischemic symptoms in patients undergoing elective PCI. The observed cardio- and renoprotection appears to confer sustained benefit on reduced major

* Corresponding author at: Cardiovascular Medicine, Assiut University, Assiut 71526, Egypt. Tel.: +20 88 2413006, mobile: +20 1094438055; fax: +20 88 2333327.
E-mail address: ayman.hassan@aun.edu.eg (A.K.M. Hassan).

Peer review under responsibility of Egyptian Society of Cardiology.

http://dx.doi.org/10.1016/j.ehj.2015.08.001

adverse events at 3 month follow-up beyond what is seen with judicious pre- and post-hydration (ClinicalTrials.gov identifier: NCT02313441).

1. Introduction

The first serendipitous description of ischemic Preconditioning in 1986 found that intermittent and short-lived non-lethal organ ischemia prior to significant ischemia–reperfusion (I–R) induced a potent form of endogenous protection in the recipient organ.[1] Remote ischemic 'pre-conditioning' and 'post-conditioning' are now well-established mechanisms of cytoprotection against ischemia–reperfusion injury, triggered by intermittent Preceding ischemia prior to [remote Preconditioning, PreC[2,3]] or after [remote post-conditioning, PostC[4,5]] the index injury. This has been reflected in preliminary clinical trials that demonstrate significant cardio- and renoprotection in various settings.[6–10]

The implementation of PreC in clinical practice has been difficult as it requires an intervention which must be implemented before the onset of ischemia. Organ ischemia might be predicted in medical interventions, such as percutaneous coronary intervention (PCI) or cardiac surgery. PreC applies brief controlled episodes of intermittent ischemia in peripheral musculature of the arms or legs to evoke the signal of remote conditioning using a simple and ubiquitous blood pressure cuff, providing a means of safely applying this protection in these patients without perceived side effects.[11]

Elective PCI is frequently associated with elevation of cardiac troponin I (cTnI) and contrast induced nephropathy (CIN).[12–14] Type 4a myocardial infarction (MI) related to PCI is defined as cTnI elevation 5 times > 99th centile of the upper reference limit.[15] PCI-related troponin elevation of this magnitude and CIN correlates with a significant increase in major adverse events (MAE).[15] Micro-embolization of plaque debris and side branch occlusion during PCI procedure[16] and cardiac reperfusion injury,[17] have been proposed as the most likely causes of PCI-related MI, with prognostic relevance.[12]

This single-center prospective non-randomized controlled trial aimed to assess the cardio- and renoprotective effect of remote PreC after elective PCI.

2. Methods

2.1. Identification and recruitment of patients

We performed a prospective non-randomized parallel group comparison at the catheterization laboratory of Assiut University Hospitals (AUH).

Patients between 18 and 80 years of age, scheduled to undergo an elective PCI and able to give an informed consent were eligible for enrollment in the study (Fig. 1, Table 1). Elective PCI was defined as any coronary revascularization in a low-risk, hemodynamically stable patient who presents to the facility for a planned PCI or for a coronary angiogram followed by ad hoc PCI. Exclusion criteria were as follows: (1) emergency PCI; (2) baseline troponin value $\geqslant$0.04 ng/mL; (3) nicorandil or glibenclamide use; (4) those who could not give informed consent; and (5) patients with severe renal impairment or on regular dialysis as described in detail previously.[18]

2.2. Study groups and protocol

Consecutive patients undergoing elective PCI between September 2013 and May 2014, were invited to participate in the study during their attendance at a routine preadmission clinic. Eligible patients, after obtaining informed consent, were systematically allocated to the PreC treatment group or the control group according to our daily based allocation technique (Fig. 1). 259 patients were screened for eligibility. Of the 259 patients screened, 18 were on nicorandil, 20 were on glibenclamide, and 11 had incomplete data. These 49 were excluded from this analysis, leaving 210 participants for systematic allocation, 10 of whom were dropped out of the study (Fig. 1). PreC was successfully provided to 100 participants without complication. Demographic and clinical details showed no difference between control and PreC groups (Table 1).

2.3. Pre- and post-procedural hydration protocols

Patients were hydrated with intravenous saline infusion as prophylaxis against contrast induced nephropathy (CIN) [3–4 mL/kg/h 4 h before and after intervention and encouraged to drink lots of water after PCI (except those with left ventricular dysfunction or sever kidney disease, who underwent hydration with 1 mL/kg/h for 12 h before and after PCI)] as described in detail previously.[19,20]

2.4. Assignment method

Participants were allocated to the treatment group by a day-dependent method of allocation. The analysis was blinded as all outcome measures were recorded by an independent researcher without prior knowledge of the study allocation of the participants. The study protocol was approved by the ethical committee of Assiut faculty of medicine (IRB no: IRB00008718 at 23 June 2013). A written informed consent was obtained from all participants. The consent form was designed with an explanation on the purpose and conduction of this research project. The study identification number at ClinicalTrials.gov.is NCT02313441.

2.5. Sample size power calculation

The sample size was determined on the basis of the primary outcome, post-PCI cTnI at 24 h. PreC was estimated to reduce the prevalence of PCI-induced cTnI release by 15% as described in detail previously.[18] A power calculation ($\alpha = 0.05$; $\beta = 0.2$; statistical power = 80%) estimated a sample size of 100 patients per group would be needed. Hence 200

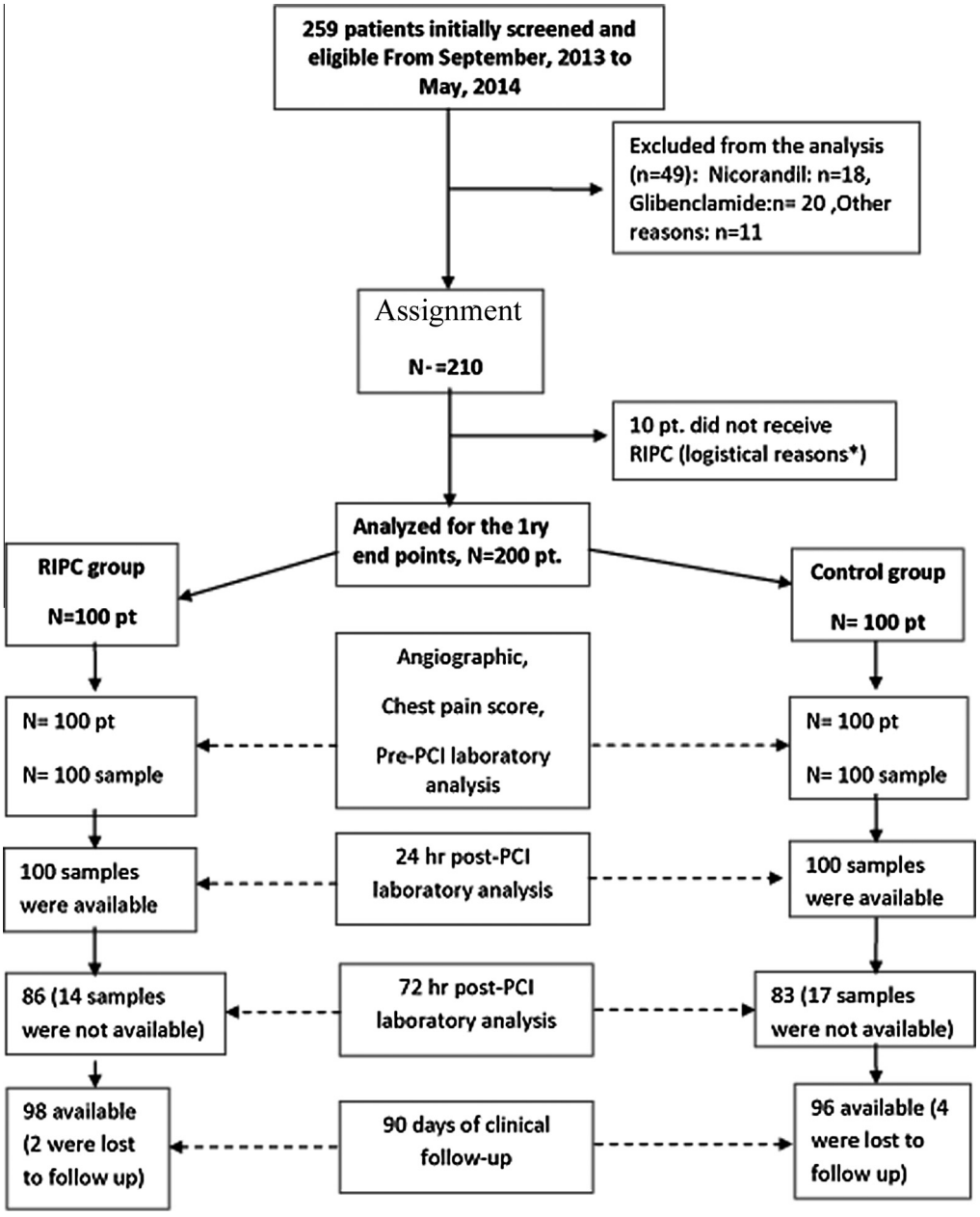

Figure 1 Flow of patients through the study. * = dropout. RIPC = remote ischemic pre-conditioning; PCI = percutaneous coronary intervention; Pt. = patients.

patients were systematically assigned into the study to enable such a reduction to be detected.

2.6. Study intervention

2.6.1. PreC and control intervention

Patients in the remote PreC had a blood pressure cuff placed on their upper arm <2 h before the PCI procedure. The blood pressure cuff was inflated to a pressure of 200 mmHg for 5 min, followed by 5 min of deflation to allow reperfusion. This procedure was repeated 3 times followed by deflation and progress to PCI as described in detail previously.[18] Control participants did not experience transient upper-limb ischemia.

2.6.2. PCI procedure

PCI was performed using femoral approach in all our patients using 6 French guiding catheters. Ultravist (iopromide; Bayer Schering Pharmaceuticals, Berlin, Germany) was used as intracoronary contrast. Participants were pre-treated with aspirin 150 mg and clopidogrel 600 mg orally before the procedure, and intraprocedural intravenous heparin bolus 10,000 IU. Glycoprotein IIb/IIIa inhibitors, stent implantation and all other medication were given at the discretion of the primary operator, adhering to best conventional clinical practice.

2.6.3. Post-procedure care

Participants were managed conventionally following PCI, as described in detail previously, including a period of in-patient

Table 1 Demographic and clinical data of participants used remote ischemic preconditioning and control groups before percutaneous coronary intervention.

Variable	Control ($N = 100$)	PreC ($N = 100$)	P
Age (years)	56 ± 10	57 ± 9	NS
Male Gender, *n* (%)	76(76%)	80 (80%)	NS
Risk factors			
Smoking, *n* (%)	45 (45%)	47 (47%)	NS
Hypertension, *n* (%)	42 (42%)	46 (46%)	NS
Dyslipidemia, *n* (%)	28 (28%)	31 (31%)	NS
Diabetes Mellitus, *n* (%)	35 (35%)	32 (32%)	NS
BMI, median (IR)	27.5 (25.4–30.2)	27.3 (25.5–30.1)	NS
History of CKD, *n* (%)	18 (18)	20 (20)	NS
Clinical details			
LVEF (%)	59 ± 9	60 ± 10	NS
Previous PCI, *n* (%)	8 (8%)	7 (7%)	NS
Previous CABG, *n* (%)	5 (5%)	6 (6%)	NS
Time since the latest angina before PCI < 24 h, *n* (%)	22 (22%)	21 (21%)	NS
Angina CCS grade III/IV, *n* (%)	23 (23%)	24 (24%)	NS
Hemoglobin (mg/dl)	12 ± 2	12 ± 3	NS
Baseline SCr, (mg/dl)	0.95 ± 0.31	0.98 ± 0.39	NS
Baseline eGFR (mL/min/1.73 m^2)	85 (64–91)	71 (64–88)	NS
Medications, *n* (%)			
Chronic aspirin therapy	94 (94%)	100 (100%)	NS
Chronic clopidogrel therapy	44 (44%)	56 (56%)	NS
ACEI or ARB	70 (70%)	68 (68%)	NS
Statins	94 (94%)	95 (95%)	NS
Beta-blockers	80 (80%)	79 (79%)	NS

Data are presented as mean ± standard deviation, number (%) of patients or median (interquartile range). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCS, Canadian Cardiology Society; CKD, chronic kidney disease; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PreC, remote ischemic preconditioning; NS, not significant; PCI, percutaneous coronary intervention; SCr, serum creatinine.

observation, with 150 mg/day of aspirin and 75 mg/day of clopidogrel for 1 month in case of a bare-metal stent and for 1 year in case of a drug eluting stent as described in detail previously.[21]

2.7. Data collection

2.7.1. Biochemical assays

Blood samples were taken on the morning of admission to the hospital, when patients had been fasting for more than 10 h (baseline), and again 24 h after PCI for serum cTnI and serum creatinine. Another venous blood sample was taken on day 3 after PCI for assessment of serum creatinine level and estimated glomerular filtration rate (eGFR).

cTnI was analyzed with an automated immunoassay (Bayer ADVIA IMS Troponin-I Ultra method, Bayer, Berlin, Germany). The 99th percentile of the cTnI level in a reference population (upper reference limit) of healthy volunteers was below the lower limit of detection of 0.04 ng/mL. The variation coefficient, a measure of precision within the analytical range, is <10%, complying with the European Society of Cardiology/American College of Cardiology consensus requirements.[22] The analytical range was 0.01–50 ng/mL, with an assay sensitivity of 0.006 ng/mL. The European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation definition of a PCI-related MI (MI 4a) was defined as >0.20 ng/mL (5 times the upper reference limit).[15] Serum creatinine was analyzed using the Dimension Xpand Plus assay (Siemens Diagnostics; upper limit of normal (ULN) = 115 μmol/L). The eGFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.[23] CIN was defined as an increase in the serum creatinine level of more than 0.5 mg/dl or more than 25% from baseline within 3 days after procedure without any other identifiable cause of acute kidney injury.[24]

All biochemical measurements were made at the end of the study by two independent researchers (M.H.M.A. & H.A.A.) without knowledge of the study allocation of the participants.

2.7.2. Peri-procedural parameters

Arterial blood pressure was measured by monitoring intra-aortic pressure through guiding catheter without guide wire. Heart rate was measured by real-time electrocardiographic monitoring at the moment of balloon inflation. Occurrences of angina (chest pain, tightness, and similar symptoms of myocardial ischemia) during PCI were assessed. Chest pain severity during PCI was graded on a scale of 0 for no pain to 10 for the most severe discomfort ever experienced. Angiographic success was defined as a residual stenosis of <15% by visual angiographic assessment and the absence of thrombosis or dissection. Procedural factors, including length and type of implanted stent, duration and pressure of coronary balloon inflations, and other variables, were recorded by an independent researcher without prior knowledge of the study allocation of the participants. Peri-procedural parameters were described and used in detail previously.[18,20]

Table 2 Angiographic and periprocedural data of participants systematically allocated to remote ischemic preconditioning and control groups.

Parameter	Control (N = 100)	PreC (N = 100)	P
Angiographic parameters			
Target vessel, *n* (%)			
LM	3 (3%)	4 (4%)	NS
LAD	45 (45%)	40 (40%)	NS
LCx	17 (17%)	20 (20%)	NS
RCA	23 (23%)	22 (22%)	NS
Combined	15 (15%)	18 (18%)	NS
Side branch > 2 mm, *n* (%)	34 (34%)	30 (30%)	NS
CTO, *n* (%)	9 (9%)	10 (10%)	NS
Subtotal occlusion, *n* (%)	14 (14%)	19 (19%)	NS
Lesion type (AHA/ACC), *n* (%)			NS
A	34 (34%)	28 (28%)	
B	37 (37%)	33 (33%)	
C	29 (29%)	37 (37%)	
PCI-related parameters			
Predilation	39 (39%)	40 (40%)	NS
Postdilation	22 (22%)	24 (24%)	NS
Number of DES	22 (22%)	24 (24%)	NS
Mean number of stents per case	1.6 ± 0.5	1.6 ± 0.7	NS
Mean stent diameter per case, mm	2.9 ± 0.7	2.9 ± 0.8	NS
Mean stent length per case, mm	31 ± 17	30 ± 17	NS
Contrast (mL)	160 ± 98	174 ± 83	NS
Glycoprotein IIb/IIIa inhibitors	22 (22%)	24 (24%)	NS
Clinical state during angioplasty			
SBP, mm Hg	135 ± 20	137 ± 17	NS
DBP, mm Hg	78 ± 12	77 ± 13	NS
HR, beats per minute	70 ± 14	71 ± 12	NS
Chest pain score > 1, *n* (%)	78 (78%)	54 (54%)	0.004
Complications, *n* (%)			
Dissection	9 (9%)	8 (8%)	NS
Jailed side branch (TIMI 0/1)	6 (6%)	7 (7%)	NS
After stent implantation, *n* (%)			
TIMI flow score 0–2	2 (2%)	2 (2%)	NS
TIMI flow score 3	98 (98%)	98 (98%)	NS

Data are presented as mean ± standard deviation, or number (%) of patients. CTO, chronic total occlusion; DBP, diastolic blood pressure; DES, drug eluting stents; HR, heart rate; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main artery; NS, not significant; PCI, percutaneous coronary intervention; RCA, right coronary artery; PreC, remote ischemic preconditioning; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.

Table 3 Serum cardiac troponin I level at 24 hours and renal function at 72 hours after percutaneous coronary intervention.

Variable	Control (N = 100)	PreC (N = 100)	P
cTnI, median (IQR) (ng/mL)	0.25 (0.03–0.91)	0.05 (0.02–0.63)	0.01
cTnI < 0.04 ng/mL, *n* (%)	25 (25%)	50 (50%)	0.005[a]
cTnI 0.04–0.12 ng/mL, *n* (%)	7 (7%)	6 (6%)	0.15[a]
cTnI 0.013–0.19 ng/mL, *n* (%)	4 (4%)	3 (3%)	0.15[a]
Incidence of MI 4a, (⩾0.20 ng/mL)	64 (64%)	41 (41%)	0.02[a]
Renal function			
Peak eGFR (mL/min/1.73 m^2)	73 (63–87)	64 (48–84)	0.001
Δ eGFR (mL/min/1.73 m^2)	−12% (0–18%)	−7% (0–14%)	0.005
Peak SCr (mg/dl)	1.2 ± 0.38	1.0 ± 0.34	0.005
Δ SCr (mg/dl)	11% (0–19%)	6.5% (0–16%)	0.01
CIN, *n* (%)	11 (11%)	4 (4%)	0.05

Data are presented as median (interquartile range), number (%) of patients, or mean ± standard deviation. CIN, contrast induced nephropathy; cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; PreC, remote ischemic preconditioning; SCr, serum creatinine. Delta (Δ), difference in mean between peak minus the baseline data.

[a] Wald test for logistic regression analysis using backward method.

2.7.3. Angiographic parameters

The target vessel characteristics and the final result of PCI (predilation, postdilation, stent diameter, stent length and number) were noted as described in detail previously.[18,20] Angiographic lesion characteristics were classified according to the modified AHA/American College of Cardiology classification.[25] Preprocedural and postprocedural assessments of coronary blood flow (Thrombolysis In Myocardial Infarction flow score) were performed.[26] Other angiographic complications occurring during PCI (artery dissection, perforation, or jailed side branch with compromised flow) and contrast dose were noted. Two interventional cardiologists categorized each case and were blinded to the participant's details and the PCI operators were blinded to the patient allocation group.

2.8. Outcome ascertainment

Patients recruitment started in September 2013 and ended in May 2014. All patients were followed up for 3 months till end of August 2014. Clinical outcome was evaluated through the monitoring of MAE occurring at any time during the follow-up as described in detail previously.[18,20,27] Death was defined as "all-cause" death at follow-up. Unstable angina/acute coronary syndrome (ACS) was defined using standard diagnostic criteria including cTnI release, ECG changes and chest pain.[15] A clinical diagnosis of heart failure (HF) during follow-up was defined as either the presence of rales in more than one-third of the lung fields that did not clear with coughing or evidence of pulmonary edema on chest radiograph. Hemodialysis as a complication of acute deterioration of renal function post-PCI was also calculated. Only the most serious event of MAE was used to calculate the cumulative MAE per patient according to the following sequence: Death > ACS > HF > Hemodialysis; this was described in detail previously.[27] MAE data were recorded by an independent researcher without prior knowledge of the study allocation of the participants.

2.8.1. Outcome measures

The primary outcome measure of the study was to assess the effect of PreC on the incidence of PCI-related MI 4a (using cTnI level) at 24 h post-PCI. Secondary Outcome Measure of the study was the incidence of CIN at 72 h after contrast exposure. Other Pre-specified Outcomes include Chest pain severity during PCI and MAE at 3 month follow-up.

2.9. Statistical methods and analysis

Statistical analysis was performed with SPSS version 16 software (SPSS Inc). Although sample size was based on the assumption of normality for the distribution of mean cTnI, the extent of skewness in the distribution observed was such that means could not be assumed to have a normal distribution. Therefore, analysis was based on nonparametric analysis with the Mann–Whitney *U*-test. Clinical outcomes were presented as Kaplan–Meier survival estimates and were compared using the log-rank test. Continuous variables were summarized as mean ± standard deviation or as median (quartiles) and compared by the Student's t-test or a Wald test for logistic regression analysis using backward method, as appropriate. Categorical data were expressed as numbers (percentages) and compared by means of a Chi squared (χ^2) test and Fisher's exact test for dichotomous variables with fewer than 5 patients in a category. A value of $P < 0.05$ was considered significant.

3. Results

3.1. Primary outcome measure

Both groups were comparable regarding baseline demographic, clinical and angiographic data (Tables 1 and 2). Subjects were eligible for the study if the baseline cTnI was below the lower limit of detection for the assay (< 0.04 ng/mL). After PCI, the median cTnI concentration at

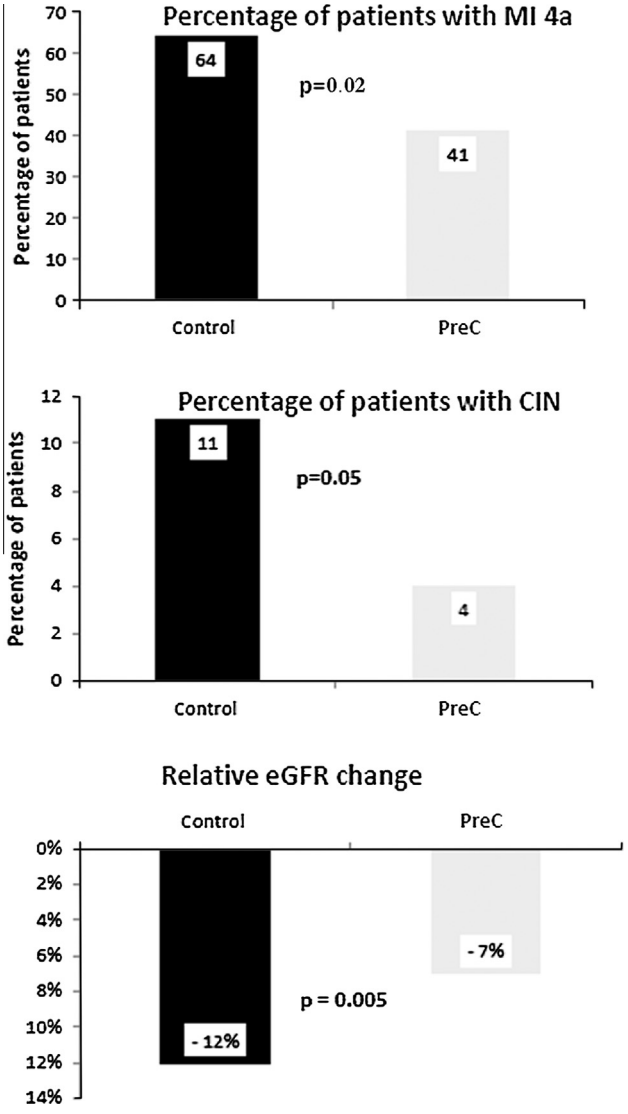

Figure 2 Study end points. Myocardial infarction, contrast induced nephropathy incidence and parameter of renal dysfunction in patients receiving remote ischemic pre-conditioning and control patients. MI4a = myocardial infarction type 4 a post-PCI, CIN = contrast induced nephropathy, and eGFR = estimated glomerular filtration rate.

Table 4 Clinical outcome and complications at 3 month follow-up in the study groups.

Variable	Control (N = 100)	PreC (N = 100)	P
Cumulative MAE[b], n	14	6	0.04[a]
Death, n	0	0	–
ACS, n	12	6	0.059[a]
HF, n	1	0	0.9[a]
Hemodialysis, n	1	0	0.9[a]

Data are presented as number of patients.
[a] Compared using Chi-square or Fisher exact test.
[b] Only the most serious event was used per patient according to the following sequence: death > ACS > HF > Hemodialysis. MAE = major adverse events; ACS = acute coronary syndrome; HF = Heart failure.

24 h was significantly lower in the PreC group: 0.05 vs 0.25 ng/mL (P = 0.01; Table 3). The incidence of MI 4a was lower in the PreC group compared with the control group (41% vs 64%, P = 0.02; Table 3, Fig. 2).

3.2. Secondary outcome measure

Renal function assessment 3 days post-PCI showed a significant trend toward lower incidence of CIN in the PreC group compared to control group (Table 3, Fig. 2). Serum creatinine increased by 11% (interquartile range: 0.0–19%) in the control group versus 6.5% (interquartile range: 0.0–16%) in the PreC group (P = 0.01, Fisher's test). The eGFR decreased from a median of 73 (interquartile range: 63–87) ml/min/1.73 m^2 in the control group to 64 (interquartile range: 48–84) ml/min/1.73 m^2 in the PreC group (p = 0.001). The decrease in the eGFR was significantly more marked in control patients compared with the PreC group (12% vs 7%, p = 0.005) (Table 3, Fig. 2).

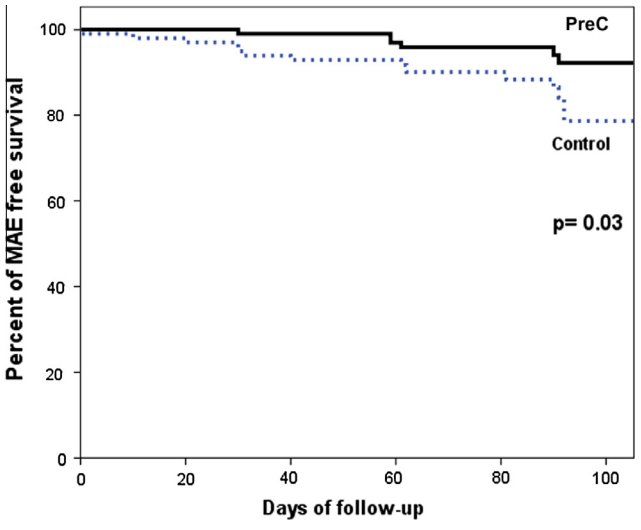

Figure 3 Kaplan–Meier graph of the major adverse events. Describes incidence of MAE over 6 months after PCI in the 194 patients with complete data (98 in the PreC group, 96 in the control group). Cox regression analysis should a hazard ratio of 0.38 (95% CI, 0.14–0.98; P = 0.03).

3.3. Pre-specified outcome measures

Subjects receiving PreC reported significantly less frequency of chest pain during stent implantation (Table 2).

Of the 200 participants 6 were lost to follow-up at 3 months. Cumulative MAE occurred in 20 patients (10%); the incidence of cumulative MAE was significantly lower in the PreC group in comparison with the control group (6% vs. 14%, p = 0.04) (Table 4). The Kaplan–Meier curves in Fig. 3 illustrate a significant trend toward a higher MAE-free survival at 3 months in the PreC group in comparison with the control group (p = 0.03).

3.4. PCI-related complications

There were no major PCI-related complications in either group (death or urgent revascularization within the first 24 h). Angiographic and PCI-related parameters, clinical details during procedure, and complication rates were similar in both groups (Table 2).

4. Discussion

The main findings in this study are as follows:

(A) PreC is easy, cheap and safe.
(B) The use of PreC < 2 h before PCI
1. reduces troponin release at 24 h post-PCI,
2. reduces type 4a MI in patients undergoing elective PCI,
3. reduces CIN at 72 h following contrast exposure, and
4. improves ischemic symptoms during PCI.
(C) PreC appears to confer a sustained benefit with reduced MAE at 3 month follow-up beyond what is seen with judicious pre- and post-hydration.

4.1. Reduction in troponin and type 4 MI

In our large prospective study, incidence of MI 4a was significantly reduced from 64% in the control group to 41% in the PreC group; this means that 23 per 100 patients undergoing elective PCI were saved from MI 4a in agreement with Luo et al.[28] where incidence of MI 4a was reduced from 54% to 39% in PreC group. Also Hoole et al.[18] found that PreC applied ~1 h before PCI increased the number of patients who had no detectable cTnI release at 24 h.

In contrast, Porto and colleagues[29] observed that PreC exacerbated cTnI release after PCI and enhanced the inflammatory response in the absence of statin therapy in low-risk patients undergoing single-vessel elective PCI.

4.2. Reduction in contrast-induced necrosis

CIN after PCI is associated with a marked increase in morbidity and mortality in short and long terms,[30] with the principal risk factor for its development being baseline renal impairment or type of contrast used.[19,24] In our study, there was a significant trend of lower incidence of CIN in the PreC group compared to control group (4 vs 11, p = 0.05). This concurs with other prior work[31] and one study[20] that showed similar ampli-

tudes of reduction in incidence of CIN (12.4% versus 29.5%). Wever et al's.[32] meta-analysis findings show that PreC effectively reduces renal damage in animals, with higher efficacy in the late window of protection. However the results of Hoole et al.[18] and Luo et al.[28] failed to show any difference in the incidence of CIN between the control and the PreC group. The potential reasons for the difference from our findings include the following: First, most of our participants had normal baseline renal function before PCI; Second, hydration for high risk patients was given according to local protocols for CIN prophylaxis; Third, more CIN occurred at 72 h than at 16 h after PCI as in Luo et al.[28] or 24 h as in Hoole et al.[18]. Yoon et al.[33] recently concluded that the remote PreC might require a considerable, rather than short, time window of ischemia.

4.3. Improvement in symptoms during PCI

Intraprocedural chest discomfort during first coronary balloon occlusion was significantly improved after PreC, in keeping with acute cardioprotection during revascularization and other studies.[18] Creating preconditioning by blood pressure cuff to cause transient ischemia of the upper limb was found to be well tolerated and to have no adverse effects.

4.4. Long-term benefit

We continued clinical follow-up for 3 months to assess whether there was a difference in hospitalization between those patients who received PreC before PCI and the control subjects. Patients who received PreC exhibited a lower MAE rate (predominantly because of a reduction in acute coronary syndromes), which comes in agreement with the data supporting the better prognosis with the lower troponin release post-PCI.[12,13] Our results are in agreement with those of Hoole et al.[18] who also demonstrated a significant reduction in the MAE rate including cardiac and cerebral events at 6 months of follow-up. Also Deftereos et al.[20] demonstrated that the 30-day rate of death or re-hospitalization for any cause was significantly reduced from 22.3% in the control group to 12.4% in PreC patients ($p = 0.05$). Furthermore, Davies et al.[34] demonstrated a sustained long-term benefit of Pre-C on clinical outcomes following PCI (around 6 years follow-up). The mechanism for this effect is unknown. Preconditioning has a beneficial platelet inhibitory and antithrombotic effect, which might stabilize vulnerable plaques, improve endothelial function, and reduce inflammation.[18] Furthermore, the effector signal-mediating myocardial protection after limb ischemia through remote IPC is not defined and appears to depend on both humoral and neuronal integrity.[18]

4.5. Prior studies

Transient limb ischemia prior to myocardial ischemia has been shown to improve the extent of necrotic reperfusion injury and endothelial function in animal models[35] and significantly reduces cardiac troponin and type 4a myocardial infarction[18,34,36] and features of reperfusion injury on cardiac MRI[37] as markers of injury in humans following revascularization for myocardial infarction. Our study results are consistent with the above research and suggest that PreC is a safe and effective strategy for providing cardioprotection when myocardial necrosis is expected.

Conversely a study where PCI was carried out immediately after preconditioning[38] found no evidence of cardioprotection. This study applied the preconditioning tourniquet ischemia for shorter periods of three minutes, which may not have been sufficient to evoke the protective signal. Also the preconditioning stimulus was applied immediately before revascularization, whereas we applied it < 2 h before intervention. Our approach allows a period for the first window of protection to be triggered, which may have been missed in the other study.

4.6. Study limitations

Based on our study assignment method, patients were allocated depending on the day they presented. This systematic allocation process may lead to bias on the basis of foreknowledge of treatment. Conversely angiographic data, laboratory analysis and follow-up results were recorded by an independent researcher without prior knowledge of the study allocation of the participants. This masking reduces the possibility of bias for all the results except for the chest pain incidence during PCI. The cTnI concentration was measured in a single blood sample obtained 24 h after PCI rather than defining the cTnI release profile every 4–6 h. The resultant value may not be the maximum plasma concentration, although it is generally accepted that the maximum concentration occurs between 12 and 24 h after myocyte necrosis. Finally the PreC was administered before < 2 h before PCI, and the time from the first cuff inflation to the first balloon dilation was not recorded in our trial.

5. Conclusion

The use of PreC < 2 h before PCI reduces the incidence of PCI-related MI type 4a, decreases the incidence of CIN and improves ischemic symptoms in patients undergoing elective PCI. The observed cardio- and renoprotection appears to confer sustained benefit on reduced MAE after PCI beyond what is seen with judicious pre- and post-hydration.

Funding

The authors received no specific funding for this work.

Conflict of interest

The authors have declared that no competing interests exist.

References

1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;**74**:1124–36.
2. Przyklenk K, Bauer B, Ovize M, et al. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993;**87**:893–9.
3. Gho BC, Schoemaker RG, van den Doel MA, et al. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996;**94**:2193–200.

4. Zhou C, Liu Y, Yao Y, et al. β-Blockers and volatile anesthetics may attenuate cardioprotection by remote preconditioning in adult cardiac surgery: a meta-analysis of 15 randomized trials. *J Cardiothorac Vasc Anesth* 2013;**27**:305–11.
5. Kerendi F, Kin H, Halkos ME, et al. Remote postconditioning. Brief renal ischemia and reperfusion applied before coronary artery reperfusion reduces myocardial infarct size via endogenous activation of adenosine receptors. *Basic Res Cardiol* 2005;**100**:404–12.
6. Ali ZA, Callaghan CJ, Lim E, et al. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation* 2007;**116**:I98–I105.
7. Botker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* 2010;**375**:727–34.
8. Cheung MM, Kharbanda RK, Konstantinov IE, et al. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol* 2006;**47**:2277–82.
9. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: underlying mechanisms and clinical application. *Cardiovasc Res* 2008;**79**:377–86.
10. Zhao ZQ, Corvera JS, Halkos ME, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 2003;**285**:H579–88.
11. Saxena P, Newman MA, Shehatha JS, et al. Remote ischemic conditioning: evolution of the concept, mechanisms, and clinical application. *J Card Surg* 2010;**25**:127–34.
12. Feldman DN, Minutello RM, Bergman G, et al. Relation of troponin I levels following nonemergent percutaneous coronary intervention to short- and long-term outcomes. *Am J Cardiol* 2009;**104**:1210–5.
13. Loeb HS, Liu JC. Frequency, risk factors, and effect on long-term survival of increased troponin I following uncomplicated elective percutaneous coronary intervention. *Clin Cardiol* 2010;**33**:E40–4.
14. Okada T, Yoshikawa D, Ishii H, et al. Impact of the first-generation drug-eluting stent implantation on periprocedural myocardial injury in patients with stable angina pectoris. *J Cardiol* 2012;**60**:264–9.
15. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;**60**:1581–98.
16. Bahrmann P, Figulla HR, Wagner M, et al. Detection of coronary microembolisation by Doppler ultrasound during percutaneous coronary interventions. *Heart* 2005;**91**:1186–92.
17. Basso C, Rizzo S, Thiene G. The metamorphosis of myocardial infarction following coronary recanalization. *Cardiovasc Pathol* 2010;**19**:22–8.
18. Hoole SP, Heck PM, Sharples L, et al. Cardiac remote ischemic preconditioning in coronary stenting (CRISP Stent) study: a prospective, randomized control trial. *Circulation* 2009;**119**:820–7.
19. Taher H Shams-Eddin, Hassan AKM, Dimitry SR, et al. Predicting contrast induced nephropathy post coronary intervention: a prospective cohort study. *Egypt Heart J* 2015;**67**:337–43.
20. Deftereos S, Giannopoulos G, Tzalamouras V, et al. Renoprotective effect of remote ischemic post-conditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2013;**61**:1949–55.
21. Hassan AKM, Hasan-Ali H, Demetry SR, et al. Early sheath removal after percutaneous coronary intervention using Assiut femoral compression device is feasible and safe. Results of a randomized controlled trial. *Egypt Heart J* 2015;**67**:69–77.
22. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined–a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959–69.
23. Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004;**141**:929–37.
24. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;**44**:1393–9.
25. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. *Circulation* 1990;**82**:1193–202.
26. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;**101**:125–30.
27. Hassan AKM, Dimitry SR, Agban GW. Can exercise capacity assessed by the 6 minute walk test predict the development of major adverse cardiac events in patients with STEMI after fibrinolysis? *PLoS ONE* 2014;**9**:e99035.
28. Luo SJ, Zhou YJ, Shi DM, et al. Remote ischemic preconditioning reduces myocardial injury in patients undergoing coronary stent implantation. *Can J Cardiol* 2013;**29**:1084–9.
29. Porto I, Blackman DJ, Nicolson D, et al. What is the incidence of myocardial necrosis in elective patients discharged on the same day following percutaneous coronary intervention? *Heart* 2004;**90**:1489–90.
30. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;**105**:2259–64.
31. 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.
32. Wever KE, Menting TP, Rovers M, et al. Ischemic preconditioning in the animal kidney, a systematic review and meta-analysis. *PLoS ONE* 2012;**7**:e32296.
33. Yoon YE, Lee KS, Choi KH, et al. Preconditioning strategies for kidney ischemia reperfusion injury: implications of the "time-window" in remote ischemic preconditioning. *PLoS ONE* 2015;**10**:e0124130.
34. Davies WR, Brown AJ, Watson W, et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP Stent trial long-term follow-up. *Circul Cardiovas Interv* 2013;**6**:246–51.
35. Kharbanda RK, Mortensen UM, White PA, et al. Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 2002;**106**:2881–3.
36. Omar AMS, Abdel-Rahman MA. Protective role of single versus multiple remote ischemic preconditioning in elective percutaneous coronary interventions. *Egypt Heart J* 2015;**67**:307–13.
37. O'Regan DP, Ahmed R, Karunanithy N, et al. Reperfusion hemorrhage following acute myocardial infarction: assessment with $T2^*$ mapping and effect on measuring the area at risk. *Radiology* 2009;**250**:916–22.
38. Prasad A, Gossl M, Hoyt J, et al. Remote ischemic preconditioning immediately before percutaneous coronary intervention does not impact myocardial necrosis, inflammatory response, and circulating endothelial progenitor cell counts: a single center randomized sham controlled trial. *Catheter Cardiovasc Interv* 2013;**81**:930–6.