International Journal of Cardiology 257 (2018) 1–6

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The EUROpean and Chinese cardiac and renal Remote Ischemic Preconditioning Study (EURO-CRIPS CardioGroup I): A randomized controlled trial

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ARTICLE INFO

Article history:
Received 2 May 2017
Received in revised form 10 December 2017
Accepted 11 December 2017

Keywords:
Remote ischemic preconditioning
Contrast-induced nephropathy
Acute myocardial injury
Diabetes

ABSTRACT

Background: The potential protective effects of remote ischemic preconditioning (RIPC) on contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI) remain to be defined.
Methods and results: A double blind, randomized, placebo controlled multicenter study was performed. Patients younger than 85 years old, with a renal clearance of 30–60 ml/min/1.73 m^2, who were candidates for PCI for all clinical indications except for primary PCI, were allocated 1:1 to RIPC or to standard therapy. The primary endpoint was incidence of CIN. The secondary endpoint was incidence of peri-procedural myocardial infarction (PMI). From February 2013 to April 2014, 3108 patients who were scheduled for coronary angiography were screened for the study. 442 fulfilled the inclusion criteria and 223 received PCI. These patients were randomized to sham RIPC ($n = 107$) or treatment group ($n = 116$). The only pre-specified subgroup of diabetic patients included 85 (38%) cases. RIPC significantly reduced CIN incidence in the overall population (12.1% vs. 26.1%, $p = 0.01$, with a NNT = 9) and in non-diabetic patients (9.2% vs. 25.0%, $p = 0.02$), but showed no benefit in diabetics (16.7% vs. 28.2%, $p = 0.21$). A trend for lower PMI was seen in the intervention arm (creatine kinase - muscle brain >5 URL; 8.4% vs. 16.4%, $p = 0.07$; troponin T >5 URL; 27% vs. 38%, $p = 0.21$).
Conclusions: Remote ischemic preconditioning significantly reduces the incidence of acute kidney injury in non-diabetic patients undergoing PCI. Larger sample size is presumably needed to assess the effect of RIPC for patients with diabetes mellitus.
Clinical Trial number: NCT02195726 https://www.clinicaltrial.gov/.

Abbreviations: CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; NAC, *N*-acetylcysteine; eGFR, estimated glomerular filtration rate; CRF, Case Report Form; CK-MB, creatine kinase-muscle brain; PMI, peri-procedural myocardial infarction.

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https://doi.org/10.1016/j.ijcard.2017.12.033
0167-5273/

1. Introduction

In present day's increasingly complex cardiac interventions [1,2], the requirement of radiographic contrast agent administration remains a relevant problem in patients undergoing procedures, due to the risk of renal insufficiency. Renal injury caused by contrast given during coronary procedures has a direct consequence on mortality. This was demonstrated in studies by Brown et al., where both transient and persistent post-procedural renal dysfunction is related to prolonged in-hospital stay and increased morbidity, mortality and costs, also during extended follow-up [3,4].

Although the pathogenesis of CIN (contrast-induced nephropathy) is not completely understood, there is increasing evidence that it occurs as a combination of direct toxicity to the renal tubular epithelium, oxidative stress, ischemic injury, and renal tubular obstruction [5–8]. Volume administration remains the key factor for the prevention of CIN, while *N*-acetylcysteine (NAC) was probably the most investigated adjunctive therapy, so far failing to demonstrate a significant clinical benefit [9–13].

The clear evidence of oxidative stress as a potential pathway for CIN has created interest regarding remote ischemic preconditioning (RIPC). RIPC directly acts on the ischemia–reperfusion mechanisms, with a demonstrated reduction in periprocedural myocardial infarctions following surgical and percutaneous revascularizations in certain cases [14,15]. Moreover, a recent pilot randomized controlled trial demonstrated the benefits of RIPC after PCI for patients at high risk of CIN, according to the Mehran Score [16,17]. This group, however, represents only a small part of those at risk, which include all patients with an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 [4]. Consequently, we performed a randomized controlled trial to evaluate efficacy of RIPC to reduce CIN after PCI in subjects with moderate renal insufficiency. According to a recent review on the topic, preconditioning efficacy appears to be decreased in animal models of type 2 diabetes mellitus, while in humans, the response according to diabetes status remains contradictory [18]. Whether conditioning is cardioprotective in the presence of comorbidities such as diabetes or hypercholesterolemia, or in the presence of co-medications, or whether the effect wanes with age, is still controversial [19]. Besides its relevant role in cardiovascular risk profile, diabetes is a well-known risk factor for contrast medium-induced acute kidney injury. We thus aimed to separately examine diabetic subjects as the only pre-specified subgroup.

2. Methods

2.1. Trial design

A prospective, randomized, placebo-controlled parallel, double-blind study, allocating patients undergoing PCI 1:1 to RIPC or control. Protocol approval was obtained by institutional ethical committee, and informed written consent was obtained from all study participants. The present study is reported according to the Consort statement [20].

2.2. Centers

The following cardiology centers were involved (in order of participation into the trial): Città della Salute e della Scienza, University of Turin, Italy (promoting Institution); Institut Cardiovasculaire Paris Sud, Hospital Jacques Cartier, Paris, France; Presidio Ospedaliero Misericordia, Grosseto, Italy; Division of Cardiology, Azienda Ospedaliera Senese, Siena, Italy; Azienda Ospedaliera S. Luigi Gonzaga, Orbassano, Italy; Ospedale Maria Vittoria, Turin, Italy; San Giovanni Bosco Hospital, Turin, Italy; Division of Cardiology, Istituto Clinico Humanitas, Rozzano, Milan, Italy; Nanjing First Hospital, Nanjing Medical University, Nanjing, China; Hospital Clinico San Carlos, Madrid, Spain; Peschiera Del Garda, Italy.

2.3. Study population

All patients undergoing percutaneous coronary angiography in a clinically stable condition were screened. Inclusion criteria were (all have to be met for inclusion): a) patients undergoing PCI for all clinical indications except those indicated for primary PCI due to STEMI, those with unstable hemodynamic presentation (such as cardiogenic shock) or those suffering from ongoing severe arrhythmias; b) patients presenting with a renal clearance in the range of 30–60 ml/min/1.73 m^2 (as assessed by the MDRD formula); c) patients younger than 85 years of age; and d) patients which are not yet recruited for other pharmacological or medical device clinical trials.

2.4. Randomization

2.4.1. Sequence generation

Randomization is generated through randomly permuted blocks of 8 patients each (www.randomization.com). List of randomization was generated for each center, and for the prespecified sub-group (i.e. patients with diabetes mellitus).

2.4.2. Implementation

Two independent researchers performed the randomization lists (G.B.Z.; F.D.A.); for each center, other cardiologists enrolled participants and assigned patients to one of the two groups.

2.4.3. Blinding

Patients were blinded to arm assignment. Moreover, both care providers (interventional cardiologist performing coronary angiography and PCI) and physicians assessing outcomes were blinded to the original arm assignment.

2.5. Sample size

The study of Er et al. [16] has shown an absolute reduction of 28% in CIN in patients at a high risk, according to the score by Mehran et al. [17]. Incidence of CIN in patients with a renal clearance of <60 ml/min/1.73 m^2 is about 25% in many contemporary registries and trials [21], and assuming a reduction of about 14%, 115 patients per group would be necessary with a power of 80% and an alpha error of 5% to assess superiority.

2.6. Data collection

Patients' clinical features, anamnesis and in-hospital procedures are collected during hospitalization by dedicated physicians. Randomization and all Case Report Form (CRF) were implemented on a dedicated website (http://www.cardiogroup.org) managed by one of the investigators (E.C.).

2.7. Study interventions

In the experimental group, patients received 5-min inflations of a blood pressure cuff to 200 mm Hg around the upper non-dominant arm for four times (as an example, the upper left arm in a right-handed patient). If systolic pressure was >150 mm Hg, inflation reached 50 mm Hg higher than baseline, followed by 5-minute intervals of reperfusion. In the control group, sham preconditioning was performed with inflation of the pressure cuff to 10 mm Hg higher than the baseline. In individuals presenting with BMI >30 kg/m^2, a dedicated blood pressure cuff for obese patients was used. Coronary angiography was performed within 45 min from last inflation.

2.8. Outcomes

2.8.1. Definition

Incidence of CIN in patients undergoing PCI represented the primary endpoint. CIN is defined as an increase in serum creatinine >0.5 mg/dl (44 mmol/l), or by a relative increase of at least 25% over the baseline value within a period of 48 h after contrast medium administration. For patients discharged the day following the index procedure, 48 h creatinine control was performed in an outpatient setting and then appraised by dedicated physicians (E-mail, fax, phone-call, ambulatory visits) [16]. Incidence of peri-procedural myocardial infarctions represented the secondary endpoint. Peri-procedural myocardial infarction is defined as an elevation of creatine kinase mioband (CK-MB) three times higher than the upper reference level limit within 48 h after PCI. Moreover, peri-procedural myocardial infarction will be adjudicated, according to recent guidelines, as an elevation of cardiac troponin (cTn) values of more than five times the 99th percentile upper reference limit (URL), in patients with normal baseline values (≤99th percentile URL), or a rise of cTn values by >20%, if the baseline values are elevated and stable or falling [22–24].

2.8.2. Adjudication

The primary and secondary endpoints were separately assessed by three researchers (E.C.; E.C.; F.D.A.) who were blinded to the assigned arm, and divergences were solved after consensus.

2.9. Statistical methods

Continuous variables were summarized as mean (SD) or median (quartiles) values and compared with the use of the Student t-test, ANOVA and Mann–Whitney test for non-parametric variables; categorical data were expressed as numbers (percentages) and compared with the use of the Chi-square test. A value of $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS version 21 (IBM software, Chicago, IL).