01.01.2018

Remote Ischemic Preconditioning and Contrast-Induced Acute Kidney Injury in patients undergoing elective percutaneous coronary intervention

Karolina Stokfisz , MD, Anna Ledakowicz-Polak , MD, PhD,

Michal Kidawa , MD, PhD, Marzenna Zielinska , MD, PhD

ID: RNN/219/13/KE
NCT03761368

Corresponding author: Karolina Stokfisz, Intensive Cardiac Therapy Clinic, Department of Invasive Cardiology and Electrocardiology, Medical University of Lodz, Pomorska 251, 2-213 Lodz, Poland, Tel/Fax. +48-42-201 42 60, e-mail: stokfisz.karolina@gmail.com

Running title: Stokfisz et al. RIPC and CI-AKI in patients undergoing elective PCI

Part 1

Project summary

We conducted prospective, randomized, sham-controlled clinical study. Data was collected between March 2015 to June 2018. 101 patients admitted to Intensive Cardiac Therapy Clinic Medical University of Lodz and scheduled for elective PCI, were randomly assigned in 1:1 ratio to either control group (n=51) or RIPC – group (n=50). RIPC prior to PCI was achieved by four cycles of 5-min inflation to 200 mmHg followed by 5-min deflation of left upper–arm cuff. Patients from control group had a deflated cuff placed on the left arm for 40 min. Authors measured serum creatinine concentration to check the occurrence of a CI-AKI within 48 - 72 hours after PCI and serum NGAL to check its level within 3 hours after procedure.

General information

- Protocol title: **Remote Ischemic Preconditioning and Contrast-Induced Acute Kidney Injury in patients undergoing elective percutaneous coronary intervention – randomized clinical trial.**
- Name and address of the sponsor/funder: **Medical University of Lodz, ul. Kosciuszki 4, Lodz.**
- Name and title of the investigator(s) who is (are) responsible for conducting the research, and the address and telephone number(s) of the research site(s), including responsibilities of each: **KS, AL contributed in main conception and design of the current manuscript as well as in acquisition, analysis and interpretation of obtained data. KS have been also responsible for drafting the manuscript and revising it critically for important intellectual content. MK contributed in acquisition, analysis and interpretation of some essential data**. **MZ contributed in conception and design of the study, interpretation of obtained data. MZ was also responsible for critical revision and final version acceptance for publication. All authors read and approved the final protocol.**
- Intensive Cardiac Therapy Clinic, Department of Invasive Cardiology and Electrocardiology, Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland, Tel/Fax. +48-42-201 42 60
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the research: non applicable.

Rationale & background information

Contrast-induced acute kidney injury (CI-AKI) is leading cause of hospital-acquired acute kidney injury and serious complication of percutaneous coronary intervention (PCI). The aim of our study was to assess whether remote ischemic preconditioning (RIPC) reduces the incidence of CI-AKI measured by serum creatinine concentration but also with the use of serum neutrophil gelatinase-associated lipocalin (NGAL) as a new potential biomarker of kidney injury.

Study goals and objectives

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)
Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Inclusion Criteria:

- aged over 18 years
- patients with stable angina pectoris
- patients admitted to Intensive Cardiac Therapy Clinic Medical University of Lodz with intention of elective CA with follow-up PCI.

Exclusion Criteria:

- history of severe injuries up to 2 months before intervention
- history of surgeries up to 2 months before intervention
- history of cancer,
- acute inflammation during hospitalization
- chronic autoimmunologic diseases
- patients needing hemodialysis
- chronic kidney disease in stage 4 or 5 (eGFR<30 ml/min/1,73m2)
- peripheral vascular disease affecting upper limbs.

Study Design

This was a prospective, single–center, double-blind, randomized, sham-controlled trial. The ethics committee of Medical University of Lodz approved the protocol (approval number: RNN/219/13/KE) and study was conducted in accordance with the Helsinki Declaration and national law. All participants provided written, informed consent before beginning of enrollment to the study. Study design, along with data collection and analysis, were all conducted solely by the authors.

Methodology

After admission to the Department, patients were randomly assigned in 1:1 ratio to either control group or RIPC – group by means of a computerized randomization table. Blinded investigator, not involved in either CA or randomization procedure, performed assignment intervention. The RIPC group underwent four cycles of 5-min inflation to 200 mmHg followed by 5-min deflation of left upper – arm cuff (in excess of further radial catheters placement). Patients from control group had a deflated cuff placed on the left arm for 40 min. The RIPC protocol began within 1 hour before CA, and was completed prior to the start of procedure. The time between the end of the last inflation of the blood-pressure cuff and placement of right radial PCI catheter was <25 min.

In accordance with guidelines, all patients received standard care for patients with stable coronary artery disease and according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines all patients received routine care for patients with impaired renal function including hydration according to the clinical state by continuous intravenous saline infusion (0,9%) - 12 hours before to 12 hours after CA with followed-up PCI (1mL per kilogram of body weight per hour) with 600mg of N-acetylcysteine (NAC) i.v. twice – 2 hours before and 12 hours after PCI, discontinuation of nephrotoxic drugs (f.e. metformin, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors and others) and the lowest possible dose of contrast medium application. Agents which can interfere with RIPC were transiently withdrawn 24 hours before the procedure (f.e. sulphonylurea). In all patients CA with follow-up PCI was performed by right radial access according to standard clinical practice. In all patients, during CA as a contrast Iomeron 400 (iomeperolum, osmolarity 726 ± 34 mOsm/kg H_2O at 37^0 C), a non-ionic low-osmolar contrast medium was used. PCI was performed according to the current ESC/EACTS Guidelines on Myocardial Revascularization.

Venous blood samples were drawn before the CA - in the admission to the hospital and at 3 and 48 hours after the procedure for measurement of serum creatinine and NGAL concentrations. We used ELISA test to measure NGAL concentration (Human Lipocalin – 2/NGAL ELISA, BioVendor). Serum creatinine levels were measured with an enzymatic assay (Crea Creatinine OSR6578, Beckman Coulter). Estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease equation: 186×(serum creatinine [mg/L])−1.154×(age [years])−0.203×(0.742 if female)×(1.210 if of African descent). The risk of developing CI–AKI was evaluated using the Mehran's risk score.

Follow-Up

Until the end of hospitalization.

Data Management and Statistical Analysis

We will performed statistical analysis using the STATISTICA 12.5 (StatSoft Inc., Tulsa, OK, USA). For all the tests we will use p = 0.05 as the statistical significance level. Categorical variables will be summarized as frequencies with percentage. Shapiro−Wilk test was will be use to assess the normal distribution of variables. Non-parametric statistics will be use when variables had other than normal distribution. Continuous variables with other than normal distribution will be expressed as medians quartile 25 (Q25), quartile 75 (Q75) with interquartile range (IQR). Correlations will be assessed by using Spearman's rank correlation coefficient. Differences between continuous variables will be compared by using Mann−Whitney *U* test. The Wilcoxon signed-rank test will be used to compare repeated measurements. To assess the suitability of NGAL values in CI-AKI occurrence probability estimation, the receiver operating characteristic (ROC) curve analysis will be performed. Using the risk reduction findings RIPC to reduce the incidence of AKI from a previous study (study power of 0.80 and α= 0.05), it was calculated that at least 50 patients were needed in each arm of the study.

Expected Outcomes of the Study

Increasing use of contrast medium in diagnostic and therapeutic procedures became a leading cause of hospital-acquired acute kidney injury (AKI) and is known as contrast-induced acute kidney injury (CI-AKI). Although high-osmolar, iodine-containing contrast media are replaced by low-osmolar agents and hydration protocols are still improving, CI-AKI is demonstrated in approximately 12% of all patients undergoing percutaneous coronary intervention (PCI) and is strictly associated with higher morbidity and mortality. Nowadays CI-AKI is defined according to serum creatinine concentration (SCr) as any of the following: (1) an absolute rise of ≥ 0.5 mg/dL (44 μmol/L) and/or (2) a relative increase of 25% in serum creatinine compared to baseline within 48 to 72 hours after contrast administration. In the era of ambulatory procedures or short-term hospitalizations this definition of CI-AKI is highly limited because it does not give a chance to diagnose CI-AKI sooner than 2 days after nephrotoxic agent application. Furthermore hydration status, may modulate SCr concentration and further complicate the diagnosis of CI - AKI. That leads to the investigation of new, better potential biomarkers of AKI which are able to show kidney injury much earlier, within few hours or even show subclinical AKI where structural kidney injury is not related with increase in SCr concentration. In the last decades, several novel biomarkers of AKI have been studied including neutrophil gelatinase-associated lipocalin (NGAL), the most investigated and the most promising. NGAL is almost undetectable in either plasma or urine in patients with a normal kidney function as well as its levels are predictive of AKI and AKI outcomes. As important as looking for a new biomarkers of AKI is

searching for novel preventive interventions. Remote ischemic preconditioning (RIPC) turned out to be one of the most promising and intriguing nonpharmacological strategy. This simple procedure consisting of brief, non-lethal episodes of ischemia and reperfusion applied in one tissue or organ protects remote tissues or organs from subsequent injury. Our prospective, randomized, sham-controlled clinical study was conducted to assess whether RIPC reduces the incidence of CI-AKI measured by standard way of using SCr concentration but also with the use of serum NGAL as a new potential biomarker of kidney injury. Furthermore, the aim of our investigation was to analyze the safety and clinical outcomes of RIPC after elective coronary angiography (CA) followed by percutaneous coronary intervention (PCI).

In the light of our study RIPC may become a easy applicable and cheap “future of nephroprotection”. Moreover NGAL may be considered as a daily used early marker of kidney damage.

Dissemination of Results and Publication Policy

The results of the study will be published.

Duration of the Project

January 2015 – December 2018

Problems Anticipated

None.

Project Management

The role and responsibility of each member of the team has been mentioned above.

Ethics

The Ethics Committee of Medical University of Lodz prospectively approved the protocol (approval number RNN/219/13/KE). Study was retrospectively registered in service of the U.S. National Institutes of Health (30 November 2018; ClinicalTrials.gov Identifier: NCT03761368). Study was conducted in accordance with the Helsinki Declaration and national law.

Informed Consent Forms

All included patients in the trial gave their written informed consent. A copy of the written consent is available for reasonable request.

Part 2

Budget

Funding: Medical University of Lodz. KS is the grant receiver.

Other support for the Project

None.

Collaboration with other scientists or research institutions: None

Links to other projects: ClinicalTrials.gov Identifier: NCT03205410

Other research activities of the investigators: as above

Financing and Insurance: Tests covered by the project protocol will be performed as part of insurance of the hospitalized patient and insurance resulting from the employment of the researches of the project.