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Does Remote Ischaemic Preconditioning Protect Kidney and Cardiomyocytes After Coronary Revascularization? A Double Blind Controlled Clinical Trial

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ABSTRACT

Objective: To investigate efficacy of remote ischaemic preconditioning on reducing kidney injury and myocardial damage after coronary artery bypass grafting surgery (CABG). **Background**: Ischaemic preconditioning of a remote organ reduces ischaemia-reperfusion injury of kidney and myocardium after CABG. **Method**: To reduce myocardial damage and kidney injury by applying Remote Ischaemic Preconditioning we recruited 100 consecutive patients undergoing elective coronary artery bypass grafting surgery. We applied three cycles of lower limb tourniquet, inflated its cuff for 5 minutes in study group or left un-inflated (sham or control group) before the procedure. The primary outcome was serum creatinine, creatinine clearance and troponin-I Levels at time 0, 6, 12, 24 and 48 h. Secondary outcomes were serum C-reactive protein, inotrope score, ventilation time and ICU stay. Data's were analyzed by MedCalc (MedCalc Software bvba, Acacialaan, Belgium). We compared the two group by student t test, chi-square and Mann-Whitney tests. **Results:** The two groups were not statistically different in terms of age, gender, smoking habits, drug use, hypertension, hyperlipidemia and diabetes mellitus. This study showed a higher CRP level in study group comparing with control group (P=0.003), creatinine clearance was slightly higher in study group specially 24 h after procedure but was not statistically significant (p=0.11). Troponin-I level was significantly lower in study group (p=0.001). **Conclusion:** This study showed a lower Troponin-I level in study group which suggest a cardio-myocyte protective function of RIPC. It also showed slightly lower Creatinine clearance in control group, gap between two group increases significantly 24 hours after procedure which may suggest a potential kidney protection by RIPC. Serum CRP level was higher in study group. A multi-center randomized controlled trial with a longer time for creatinine clearance measurement may show the potential effectiveness of this non-invasive inexpensive intervention on reducing kidney injury after CABG.

Key words: Ischaemic preconditioning; Complications; Cardiac Surgical Procedures, Coronary artery bypass grafting surgery.

1. BACKGROUND

Ischaemic heart disease is the commonest cause of death in many countries, including Iran and coronary artery bypass grafting surgery (CABG) is one of the few treatment options for these patients (1).

For on-pump coronary artery bypass grafting surgery we cross-clamp the ascending aorta and consequently deprive cardiomyocytes of oxygenated blood, after surgical procedure releasing the cross-clamp

induce abrupt tissues re-oxygenation and can cause ischemia/reperfusion injury (2).

This process can initiate an inflammatory response and produce oxygen free radicals, resulting a microvascular and endothelial cell dysfunction, increase risk of vasospasm, vascular thrombosis and accelerated atherosclerosis (3, 4). It may also induce cerebrovascular accidents, myocardial dysfunction and arrhythmias, multi-organ system dysfunction such as respiratory renal or gastrointestinal dysfunction (5-7).

To reduce ischemia-reperfusion organ injury, various treatment modalities have been used, such as leukocyte depletion therapy, anti-oxidant therapy, and complement therapy (8). One of the effective measures used in this regard is ischaemic preconditioning, in which a brief periods of ischemia followed by reperfusion adapts the cardiac tissue to a longer ischaemic time and protects myocardium against adverse effects of ischaemic/reperfusion injury (9, 10, 15). Although the exact mechanism of RIPC is not clearly identified, some factors such as nitric oxide (NO) or adenosine release seems to play a fundamental role in this phenomenon (3). Some authors have proposed that the effect of ischaemic preconditioning may be transient, but animal studies have indicated that the protective role of RIPC can last 24 hours after surgery (3, 11).

In RIPC, ischemia is induced through limb tourniquet (12-14) and has been used in various surgical procedures and even in patients undergoing percutaneous coronary intervention (15). There is still controversy regarding the beneficial effects of RIPC, on duration of hospital stay rate of mortality, myocardial infarction, stroke and renal dysfunction.

As renal and cardiomyocyte dysfunction are the most important adverse effects of CABG, role of RIPC on reducing renal complications and myocardial dysfunction has been addressed in the present study.

2. METHODS

Study design

This double-blind randomized clinical trial was conducted in Mazandaran Heart Centre a tertiary referral university hospital on patients who underwent CABG from March 2013 to February 2015. The protocol of the study was approved by Mazandaran University of Medical Sciences research council and ethical committee and was registered at www.irct.ir (IRCT138903123646N3). The design and objectives of the study were explained to all participants and written informed consent was obtained. The CONSORT (Consolidated Standards of Reporting Trials) recommendations for reporting randomized controlled clinical trials were followed (Figure1).

Participants

We included patients undergoing non-emergency on-pump CABG surgery with ejection fraction (EF) higher than 35%. Exclusion criteria were under age under 18 years, CABG with valve surgery, pregnancy, advanced liver disease (INR >2.0), severe renal impairment (Creatinine clearance <50 ml/min), respiratory failure (O_2 Sat <90 %), acute myocardial infarction up to 14 days before surgery, advanced lower limb vascular disease, and patients using Sulfonamide or Nicorandil.

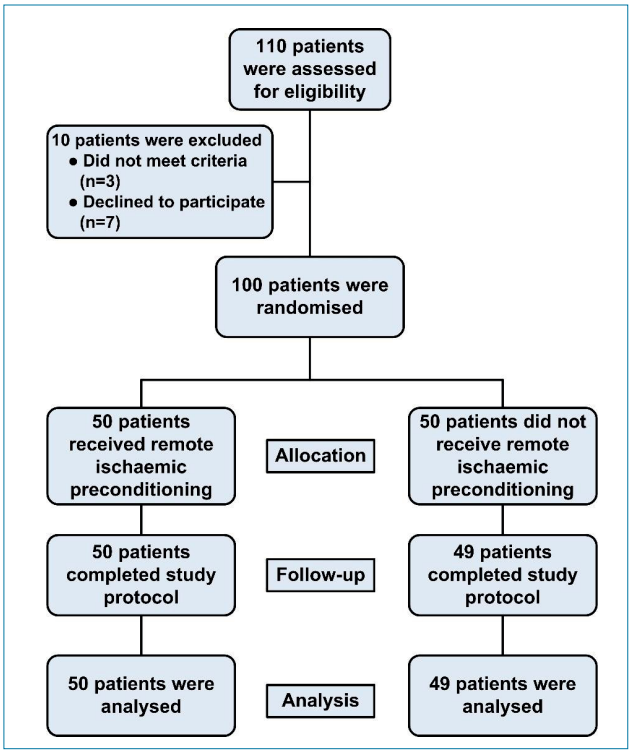

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow through the trial

Procedures

We used a combinations of midazolam, sufentanil and pancuronium bromide for induction of anesthesia. All patients were mechanically ventilated using oxygen via an endotracheal tube. We maintained anesthesia with a moderate doses of sufentanil and midazolam. Also used isoflurane (<1%) or/and propofol (25-100 μg /min) as a supplement. Muscle relaxation was maintained with cisatracurium. Invasive arterial blood pressure, central venous pressure, O_2 saturation, end tidal CO_2, five leads ECG and nasopharyngeal temperature were monitored continuously. Intravenous glyceryl trinitrate was administered during anesthesia (20–70 μg/min) only when clinically indicated, since it may interfere with RIPC. The surgical procedure was started with Median sternotomy, after preparing left internal thoracic artery patients were put on bypass draining the right atrium and returning to the ascending aorta. The initial dose for Heparin was 300 IU/kg to achieve an activated clotting time (ACT) of >480 s. Heparin was reversed using a full dose of protamine chloride returning activated clotting time (ACT) to or <120 s. We used a Non-pulsatile CPB circuit with uncoated tubes, a membrane oxygenator, and an open reservoir. For priming the CBP circuit we used a Colloid based (Voluven) solution with no blood or even blood products. The maximum and minimum Hct levels were 24% and 20%, respectively. With a moderate hypothermia (32 °C) we maintained a mean arterial pressure of 60 to 80 mmHg during CPB. Arterial blood gas was managed using anα-Stat *P*H monitoring. After induction of anesthesia and before skin incision, Remote ischaemic preconditioning was induced by 3 cycles (each

cycle 5-minutes) of a tourniquet cuff inflation applied to upper thigh (≥20mmHg higher than the resting systolic arterial pressure) followed by 5-minute reperfusion. For the sham or control group, the tourniquet was placed on the upper thigh, manipulated but inflated for the same period of time. At this period of time the lower limb was covered by a sterile sheath and inflation of tourniquet was done by one individual registered nurse responsible for randomization.

3. OBJECTIVES AND OUTCOMES

Primary outcome

The study primary outcome was acute kidney injury (AKI). Serum creatinine, and Troponin I level were measured at times 0, 6, 12, 24 and 48 h postoperatively measured with the Elecsys 2010 Chemistry Analyzer (Hitachi Corp., Tokyo, Japan). Normal value for Troponin I was equal or less than (≤ 0.3 ng.mL-1). AKI was measured using Acute Kidney Injury Network (AKIN) criteria:

Stage 1: serum creatinine rise of ≥0.3 mg/dL or 150%–200% of baseline and/or urine output <0.5 mL/kg/h for >6 contiguous hours.

Stage 2: serum creatinine rise of 200%–300% of baseline and/or urine output <0.5 mL/kg/h for >12 contiguous hours.

Stage 3: serum creatinine rise of >300% of baseline or serum creatinine ≥4 mg/dL with an acute rise of at least ≥0.5 mg/l and/or urine output <0.3 mL/kg/h for >24 h or anuria for 12 h.

Secondary outcomes

Serum Troponin-I level, Dialysis, serum CRP and inotrope requirement (measured before and at 6, 12, 24 and 48 hours after surgery),ventilator time, length of ICU stay, in-hospital mortality also were considered as secondary outcomes.

Statistical analysis

Based on the assumptions of a 25% incidence for post-CABG AKI and myocardial damage and 80% effect size for RIPC we calculated a sample size of 50 for our study group. We used (GraphPad StatMate; GraphPad Software Inc; San Diego, CA, USA) software for computer randomization by means of sequentially-numbered sealed envelopes. One registered nurse who did the randomization, treatment allocation and delivering RIPC was aware of patient group, other investigator, data collector, statistician, patients and doctors were blinded to study group.

We compared the two groups with Students t-test for unpaired data or Mann-Whitney U test comparing medians with interquartile ranges, depending on the normality of the distribution. Categorical data were expressed as frequencies and were compared using x^2 or Kruskall-Wallis statistics. Statistical analysis was performed using MedCalc (MedCalc Software bvba, Acacialaan, Belgium) and in all cases p<0.05 was considered statistically significant.

4. RESULTS

The RIPC was administered to all patients in study group with no distal arterial or venous complications.

Randomization Group	Control (n=49)	rIPC (n=50)	p-value
Age (years)	61.2±8.1	59.5±8.0	0.28
Male sex	33 (67)	37 (74)	0.51
Body Mass Index (Kgm^{-2})	27.7±4.1	27.6±3.7	0.87
Mean Arterial Pressure (mm Hg)	89±14	88±14	0.73
Resting heart rate (bpm)	80±16	77±13	0.26
Opium addiction	12 (24.5)	11 (22)	0.82
Euro-Score	3.5±1.8	3.3±1.9	0.57
CARE score			
1	4 (8)	3 (6)	0.74 *
2	27 (55)	26 (52)	
3	18 (37)	20 (40)	
4	0	1 (2)	
NYHA class			
I	15 (31) `	12 (24)	0.66 *
II	28 (57)	33 (66)	
III	6 (12)	5 (10)	
Left Ventricular Ejection Fraction	50±8	51.5±6.7	0.31
Comorbidities			
Diabetes mellitus	28 (57)	18 (36)	0.54
Hypertension	31 (63)	30 (60)	0.87
Hypercholesterolemia	28 (57)	27 (54)	0.84
Smoking history			
Smoker	7 (14)	13 (26)	0.35 *
Ex-smoker	12 (24.5)	11 (22)	
Non-smoker	30 (61.2)	26 (52)	
Drug history			
Aspirin/Clopidogrel	37 (76)	33 (66%)	0.38
Beta-blocker	28 (57.1%)	30 (60%)	0.95
Calcium channel blocker	15 (30.6%)	10 (20%)	0.25
ACE-I/A_2RA **	21 (42.9%)	24 (48%)	0.69
Long-acting nitrates	20 (38.8%)	27 (54%)	0.16
Statin	33 (61.13%)	37 (74%)	0.51
Warfarin	6 (12.2%)	6 (12%) 1	1.0

Table 1. Patient characteristics. * Kruskal-Wallis test ** Angiotensin Converting Enzyme Inhibitor /Angiotensin-2 Antagonist

Randomization Group	Control (n=49)	rIPC (n=50)	p-value
Details of surgery			
Bypass time (min)	67.3±9.6	66.2±9	0.54
Cross-clamp time (min)	42.2±8.6	40.7±8.3	0.35
Number of grafts			
One	1 (2%)	0	0.78 *
Two	7 (14)	8 (16)	
Three	19 (39)	20 (40)	
Four	22 (45)	22 (44)	
Maintenance Anaesthesia			
Propofol	26 (53)	23 (46)	0.74 *
Isoflurane	18 (37)	20 (40)	
Combination	5 (10)	7 (14)	
Glyceryl trinitrate	11 (22)	14 (28)	0.66
Acute Kidney Injury **			
Stage 1	10 (20.4%)	6 (12%)	0.29
Stage 2	2 (4.1%)	1 (2%)	0.62
Total	12 (24.5%)	7 (14%)	0.21
Ventilator time (Hours)	8.41±2.34	8.70±2.30	0.53
Length of ICU stay (days)	2.69±0.65	2.76±0.65	0.61
Renal dialysis	0	0	
In-hospital mortality	0	0	

Table 2. Treatment details and outcomes., * Kruskal-Wallis test, ** AKIN Criteria

The two groups were statistically comparable in respects of age, gender, body mass index, Euro score, Care score,

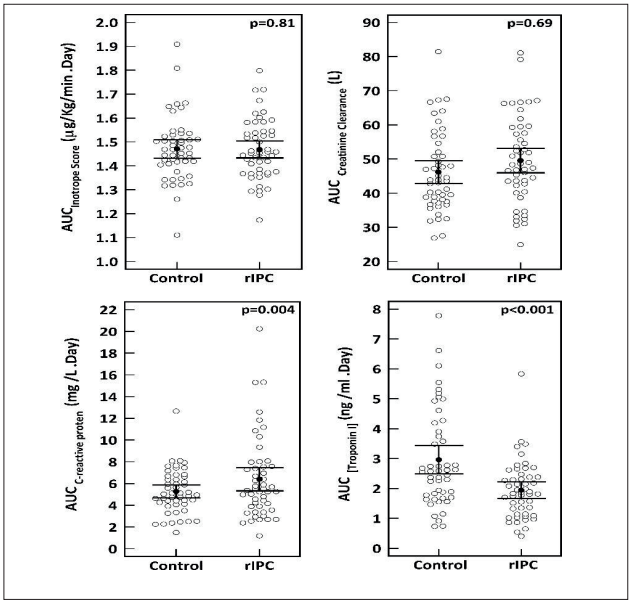

Figure 2. Serum Troponin-t and CRP levels, inotrope score and Creatinine clearance in study and sham group

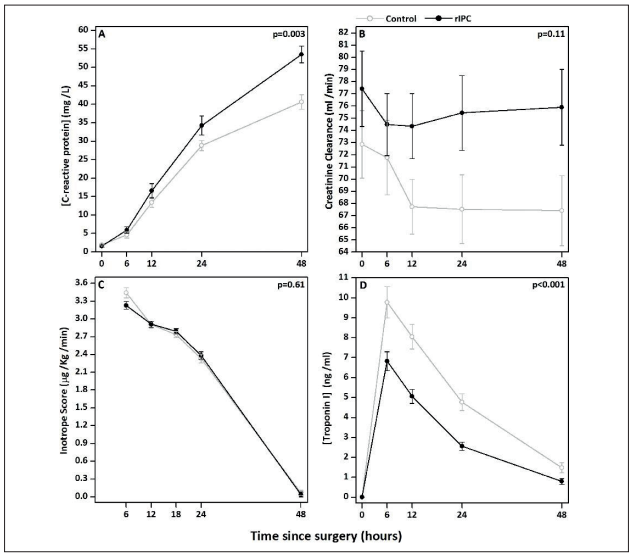

Figure 3. Creatinine clearance, serum CRP level, serum Troponin-T and inotropic score

NYHA class, hypertension, hyperlipidaemia, diabetes mellitus and drug history (Table 1).

Peri-operative data such as cross clamp time, bypass time, number of grafts, and anesthetic drugs used were comparable in two groups. Both group received Propofol, Isoflurane and GTN with no statistically significant difference. Ventilation time and ICU stay were equal in two group. There was no need for renal dialysis and there was no peri-operative or 30 days mortality (Table 2).

Serum Troponin-T level was higher in sham group which was statistically significant (p≤0.001) (Figure 2). Creatinine clearance was slightly higher in study group, the gap between two group became wider after 24h but this was not statistically significant (p=0.69) (Figure 2). Inotropic score was identical in two group (p=0.81) but serum CRP level was higher in study group (p=0.004) (Figure 2).

The mean inotrope use was 3.2 (μg/kg/min) started six hours after surgery, reducing 12 hours after surgery and returned to none after 48 hours (Figure 3). There is no statistically different rate of inotrope use in two groups (p=0.61).

Creatinine clearance was slightly higher in study group, the difference become higher after 12 hours and remained same up to the last sample but the difference between two groups was not statistically significant(p=0.11)(Figure 3).

Troponin I level was zero in the first sample in two groups made a peak six hours after surgery and returned to normal 48h after surgery. The difference between two groups was statistically significant (p=0.001) (Figure 3). Serum C-Reactive protein was higher in study group (p=0.003).

5. DISCUSSION

Our study indicate that remote ischaemic preconditioning can reduce cardiac and potentially reduce renal complications after CABG surgery. It showed a lower serum Troponin-I levels in the group received RIPC against control group, also showed a lower creatinine clearance 24 hours after surgery in control group but this was not statistically significant.

Previous studies had a contradictory results regarding the role of RIPC on reducing cardiac and renal complications after cardiac surgery.

The clinical efficacy of RIPC was investigated by Cheung and colleagues. They showed a lower serum troponin-I level and lower airway resistance in 37 children with congenital heart disease undergoing cardiac surgery receiving four cycles of 5-minutes lower limb ischemia (cuff inflated 15 mm Hg above systolic blood pressure) (16). Venugopal and colleagues have assessed the effect of three 5-minute cycles of brachial artery occlusion (Cuff inflated up to 200 mm Hg) on reducing myocardial damage in 23 CABG patients comparing with 22 patients in control group by measuring Troponin-T levels in these patients. They showed a lower troponin-T in subjects receiving RIPC (17).

Thielmann and colleague have investigated effect of RIPC on reducing myocardial damage on 27 patients in study group comparing with 26 patients in control group by applying 3 cycles of five minutes upper limb ischemia in study group on patients undergoing CABG using crystalloid cardioplegia. They also showed a lower serum Troponin-I levels in study group (18).

Karami and colleagues have examined the clinical efficacy of RIPC by applying 3 cycles of five minutes upper or lower limb ischemia on patients undergoing elective CABG and showed Troponin-I rise in study and control group.

The finding of our study is similar to Cheung, Venugopal and Thielmann but it is different in two important ways. We used the lower limb for RIPC and our study was done on adult population of patients.

Regarding the renal-protective effect of RIPC, Venugopal and colleagues have reported lower acute kidney injury (AKI) in patients receiving RIPC before cardiac surgery (18). Zarbock and colleagues randomized 240 patients with high risk for AKI to receive 3 cycles of

5-minute ischemia in one upper arm before cardiac surgery and have reported reduced rate of AKI in the RIPC group (37.5 vs 52.5%) (19). Candilio and colleagues have also compared the effect of simultaneous arm and thigh cuff inflation in two groups of 90 patients undergoing elective CABG and have reported 48% reduction in the incidence of AKI also showed lower serum troponin-T level in the RIPC group (20).They have reported reduction in the serum creatinine level 12 hour after surgery but in present study serum creatinine level dropped 24 hours after surgery. This might be due to different surgical procedures and study population. We have excluded concomitant valve surgery from our study population while Candilio's have included them.

Pedersen randomized 105 children undergoing cardiac surgery for complex congenital disorders to receive RIPC by 4 cycles of 5 minutes inflating a cuff on lower limb to 40 mm Hg above the systolic pressure and showed no renal protection in RIPC group (21). Gallagher also randomized 86 patients with pre-existing chronic kidney disease to receive three 5-minute cycles of forearm ischemia prior to CABG and have reported no difference in the incidence of AKI in RIPC group (22).

Li L in a review study indicated that the main reason for the contradicting results in RIPC studies is different definition for AKIA(23). Brevoord also reviewed the literatures for renal protective role of RIPC after heart surgery. He also concluded no difference between RIPC and control group. He indicated that as serum creatinine is the mostly used biomarker for detecting AKI (23-25), which might not change significantly in an acute setting. we have also observed its significant decrease after 24 hours. Moreover, the different protocols of RIPC causes difference in the results, as the upper limb may be less effective than the lower limb and the pressure of the inflated cuff and the frequency of courses also play a role in this difference. Besides, the different surgical procedures also affect the results, as Walsh and colleagues have indicated that renal protective effect of RIPC is only positive in the presence of cardioplegia (26). In addition, the difference in the demographic characteristics of patients, besides different inclusion and exclusion criteria also causes this diversity, as some studies have assessed children and some have assessed patients with existing renal risk, which affect the results profoundly.

Regarding the evident controversy in the role of RIPC on renal and cardiac complications of cardiac surgery, more studies are needed to establish the exact effect and the possible adverse effect of RIPC, but it's essential to use a standard definition for AKI for the results of different studies to be comparable. Moreover, the different methods of RIPC have to be compared and a standard method should be introduced, as each study has used its own method, which has caused the results not to be easily comparable with each other.

The strengths of the present study included randomizing subjects into two intervention and control groups that besides excluding many factors caused limitation in confounding factors. Moreover, this issue has rarely been addressed in Iranian studies. Beside the strengths, this study was not also free of limitations. Although the patients were randomized into the groups, it would be more optimal to select patients from different centers, in order to omit any bias and increase the generalizability of the data. Besides, the surgical procedure has to be standardized or performed by one surgeon, which was not possible in our center.

6. CONCLUSIONS

The results of the present study indicated decrease in the serum levels of creatinine 24 hours after CABG in the RIPC group, which indicates the superiority of this non-invasive inexpensive intervention in controlling the important complications of cardiac surgery.

• Conflict of interest: none declared.

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