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Remote Ischemic Preconditioning is a Safe Adjuvant Technique to Myocardial Protection But Adds No Clinical Benefit After On-Pump Coronary Artery Bypass Grafting

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ABSTRACT

Background: To evaluate the impact of remote ischemic preconditioning (RIPC) on clinical outcome, biological markers of myocardial injury, and its safety in patients undergoing on-pump coronary artery bypass grafting (CABG).

Material and Methods: This study was conducted at Ch. Pervaiz Elahi Institute of Cardiology (CPEIC) in Multan. The study took place from March 2012 to June 2013. Patients were randomly placed into two groups. Group A (N = 32) did not undergo RIPC; Group B (N = 35) received RIPC after induction of anesthesia. Similar standard general anesthesia, cardiopulmonary technique, myocardial protection strategies, and surgical techniques were used in both groups except the protocol for RIPC. Following postoperative outcome, i.e. cardiac defibrillation after removal of aortic cross clamp during the period of rewarming, demand for intra-aortic balloon pump (IABP), demand for antiarrhythmic before leaving the operation room, postoperative creatine kinase-myocardial band (CK-MB) level (at 1h, 12h, 24h, and 48h after surgery), postoperative serum creatinine level on first postoperative day, postoperative ejection fraction (EF) on third postoperative day, in-hospital mortality, and one-year mortality were noted, prospectively. Safety of protocol of RIPC was estimated by limb ischemia monitored by pulse oximetry during and after procedure of RIPC and postoperative neurapraxia by nerve examination of right upper limb.

Results: Post aortic cross clamp release cardiac defibrillation, demand for IABP, demand for high inotropes, and use of antiarrhythmic in the operation room were statistically insignificant in the non-RIPC and RIPC group with *P* values of .54, .78, .16, and .16, respectively. Mean postoperative CK-MB level (IU/L) showed the following results: At 1h (Group A 20.94 + 1.66, Group B 20.57 + 1.54, *P* = .35), at 12h (Group A 27.13 + 1.85, Group B 28.05 + 3.04, *P* = .135), at 24h (Group A 27.63 + 1.7, Group B 27.85 + 2.2, *P* = .63), and at 48h (Group A 22.95 + 2.76, Group B 23.27 + 3.6, *P* = .69). First postoperative day serum creatinine (Group A 1.29 + 0.395, Group B 1.33 + 0.57, *P* = .77) and postoperative ejection fraction percentage on the third postoperative day (Group A 50.78 + 8.72, Group B 50.57 + 8.38, *P* = .92) showed no statistical difference between two groups. Postoperative low cardiac output state, in-hospital mortality, and one-year mortality also were statistically insignificant between the groups with *P* values of .93, .29, and .33, respectively. None of the patients in either group showed evidence of limb ischemia and neurapraxia of the right upper limb.

Conclusion: RIPC is a safe technique, but it does not have additional clinical benefit after on-pump CABG surgery in the presence of a standard myocardial protective strategy.

INTRODUCTION

Ischemia during aortic cross-clamp and ischemic reperfusion injury after removal of an aortic cross clamp in on-pump CABG is an unavoidable reality despite the well-established protocols of myocardial protection. At a cellular level, ischemia/reperfusion injury results in myocardial cellular apoptosis or necrosis. Clinically, it presented as myocardial stunning with low cardiac output and difficult weaning from cardiopulmonary bypass (CPB) [George 2008]. Novel pharmacological and non-pharmacological strategies are being investigated to make myocardium more resistant to inevitable ischemia/reperfusion injury. Remote ischemic preconditioning (RIPC) is among these.

Role of RIPC in myocardial protection and reduction in ischemia/reperfusion injury is shown by experimental studies [Przyklenk 1993; Birnbaum 1997]. Direct transient arterial occlusion of gut, renal, coronary, or limb vessels have been utilized to produce transient tissue ischemia and thus the phenomena of remote ischemia/reperfusion in these experimental evidences. Complex humoral, neural, and cellular mechanisms are implicated to explain the mechanism of action of RIPC. A number of humoral factors like adenosine, bradykinin, erythropoietin, nitric oxide delta 1-opioid, etc. produced from ischemic tissue during RIPC and their systemic spread is found to protect distant organs from subsequent ischemic and ischemic reperfusion injuries [Liem 2002; Diwan 2008; Chen 2005; Weinbrenner 2002; Patel 2002]. Cellular mediators (KATP channels, calcitonin gene-related peptide, free radicals, and neural pathways) also are described to be involved in organ protection in mechanism of RIPC [Kristiansen 2005; Xiao 2001; Gho 1996]. Cardioprotective role of RIPC is interpreted by measuring the quantitative release of a biological marker of myocardial injury (CK-MB, Troponin T, Troponin I, or myocardial infarct size) after RIPC in these experimental studies.

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Based on the results of these experiments, clinical studies were conducted with the primary focus on the quantitative measure of the biological marker of myocardial injury as a primary outcome and to define cardioprotective efficacy of RIPC. Non-invasive limb ischemia with blood pressure cuff inflation above systolic blood pressure was utilized in these clinical studies to produce RIPC. Clinically important and measurable outcomes like postoperative ejection fraction, low cardiac output state, postoperative arrhythmia, operative mortality, and long-term mortality are less focused in these trials. The objective of this random trial is to address the impact of RIPC on these clinically meaningful outcomes and safety of technique utilized to produce RIPC with blood pressure cuff inflation.

METHODS

After approval from the ethical committee of CPEIC, 69 patients were recruited for the study. The study began March 3, 2012. Patients were referred from the Department of Cardiology after completing a coronary artery disease work up. All patients were experiencing Class III angina, triple vessel coronary artery disease, and American College of Cardiology (ACC) and American Heart Association (AHA) Class I indications for CABG. Informed consent was taken and patients were randomly sorted into two groups. Group A included 32 patients as a control group; Group B included 35 patients who underwent RIPC. Patients' baseline characteristics (age, gender, weight, and height) and risk factor (Canadian Cardiovascular Society angina class, diabetic status, hypertensive status, family history of ischemic heart disease, smoking, and ejection fraction) were noted. RIPC was done with the blood pressure cuff creating an occluding pressure of 200 mmHg for five minutes on the right arm in Group B. Three cycles of RIPC was done with in-between rest periods of five minutes after the induction anesthesia for CABG. For the control group, the blood pressure cuff was applied without creating any occluding pressure. The CABG operations were performed with conventional methods. Oral Bromazepam (3 mg) was administered to patients the night before surgery. Anesthetic induction was done with intravenous morphine (0.1 mg/kg), Midazolam (0.05-0.1 mg/kg), and Propofol (1.0-2.5 mg/kg). Atracuronium (1 mg/kg) was used as a paralyzing agent before endotracheal intubation. Anesthesia was maintained with Sevoflurane/isoflurane. The CPB was established with aortic and two-stage right atrial cannula. The CPB circuit was primed with crystalloid Ringer's solution. Heparin was administered at 300 U/kg to achieve an ACT > 600 sec. Systemic temperature was kept at 30°C. The local cooling was done with local ice slush. Cold blood cardioplegia was delivered through the ascending aorta and was repeated every 20 minutes. The initial dose of cardioplegia was 15 mL/kg, and the next dose was given as 7 mL/kg. Hemofiltration was used to maintain hematocrit levels between 22% and 28%.

Surgery was performed by a consultant cardiac surgeon with a minimum 10 years of experience. In all patients, left internal mammary artery (LIMA) and saphenous vein were used as a conduit for coronary bypass. After coronary anastomosis, the following parameters were noted before patients left the operating room: CPB time, cross-clamp time, difficult weaning demanding IABP or high inotropic support (> 0.1microgram/kg/min of adrenaline, dobutamine, or noradrenaline), cardiac defibrillation during the period of rewarming, and use of antiarrhythmics. Any major surgical event, such as a major cardiac surgical injury, revision of graft, and aortic cross-clamp time of more than 100 minutes, excluded the patient from study. After weaning from CPB and chest closure, patients were moved to cardiac surgery ICU. They were electively ventilated for 3 hours and routine extubation was performed. During the postoperative period, CK-MB levels (IU/L) were measured at postoperative hours 1, 6, 12, and 24. Low cardiac output state demanding high inotropic support (> 0.1 microgram/kg/min of adrenaline, dobutamine, or noradrenaline), serum creatinine level the first postoperative day, postoperative EF on the third postoperative day, and in-hospital mortality was noted. Patients were followed for one year after surgery. Safety of protocol of RIPC was evaluated by limb ischemia monitored by pulse oximetry after protocol of RIPC and postoperative neurapraxia by nerve examination of the right upper limb.

RESULTS

Microsoft Excel 2007 and SPSS version 16 were used to analyze data. Baseline characteristics of patients in both groups are shown in Table 1. There is no statistical difference between the groups with regard to age, gender distribution,

Table 1. Baseline characteristics of Groups A and B

Characteristics	Group A (N = 32)	Group B (n = 35)	*P*
Age (years)	55.16 + 10.95	54.46 + 8.83	.775
Gender			
Male	78.12% (N = 25)	77.14% (n = 28)	.92
Female	21.88% (n = 7)	22.84% (n = 8)	
Height (cm)	165.41 + 11.21	163.2 + 8.95	.379
Weight (kg)	71.5 + 13.43	72.34 + 14.88	.808
Diabetes	53.13% (n = 17)	51.43% (n = 18)	.88
Hypertension	50% (n = 16)	54.29% (n = 19)	.73
History of smoking	43.75% (n = 14)	42.85% (n = 15)	.94
History of family IHD	34.38% (n = 11)	34.29% (n = 12)	.42
EF (%)	51.25 + 9.07	50.29 + 8.99	.66
Preoperative Serum Creatinine (mg/dl)	1.05 + 0.21	1.12 + 0.27	.24
Preoperative CK-MB (IU/L)	9.3 + 1.45	9.64 + 1.95	.41
Previous history of MI	25% (n = 8)	22.86% (n = 8)	.84
Cross-clamp time (min)	66.31 + 23.60	65.69 + 19.65	.906
CPB time (min)	105.53 + 28.82	110.09 + 32.01	.542

weight, height, diabetic status, hypertensive status, smoking history, family history of IHD, ejection fraction, previous history of myocardial infarction, preoperative serum creatinine, preoperative CK-MB levels, etc. In all patients, LIMA grafting to left anterior descending (LAD) were used. All patients received three bypass grafts. Mean CPB time and cross-clamp time also were non-significant in both groups.

In Group A, 9.37% of patients were defibrillated to get off from CPB. In Group B, it was 14.28%, *P* = .54. Also, 9.37% of Group A patients needed IABP after CBP compared with 11.43% patients in Group B, *P* = .78.3. Thirteen percent of patients in Group A needed antiarrhythmic agents before leaving the operating room compared with 8.57% in Group B, *P* = .16. Mean postoperative CK-MB levels (IU/L) of the two groups were as follows: 1h (Group A 20.94 + 1.66, Group B 20.57 + 1.54, *P* = .35); 12h (Group A 27.13 + 1.85, Group B 28.05 + 3.04, *P* = .135); 24h (Group A 27.63 + 1.7, Group B 27.85 + 2.2, *P* = .63); and 48h (Group A 22.95 + 2.76, Group B 23.27 + 3.6, *P* = .69). Postoperative mean serum creatinine on the first postoperative day was 1.29 + 0.395 in Group A and 1.33 + 0.570 in Group B, *P* = .77. Postoperative EF in Group A was 50.78 + 8.72; Group B was 50.57 + 8.38, *P* = .92. Low cardiac output state was 6.25% in Group A and 5.71% in Group B, *P* = .93. In-hospital mortality was 3.13% in Group A and 0% in Group B, *P* = .29. One-year mortality was 0% in Group A; it was 2.85% in Group B, *P* = .33. No patients in either group showed evidence of limb ischemia and neurapraxia of the right upper limb. The above mentioned findings in clincial outcome are summarized in Table 2.

Table 2. Clinical outcome

Outcome	Group A (n = 32)	Group B (n = 35)	*P*
Defibrillation on weaning from CPB	9.37%(N = 3)	14.28%(N = 5)	.54
IABP	9.37%(n = 3)	11.43%(n = 4)	.78
Demand for high inotropic support	8.57%(n = 3)	3.13%(1)	.16
Antiarrhythmics	3.13%(1)	8.57%(n = 3)	.16
CK-MB at 1h(IU/L)	20.94+1.66	20.57+1.54	.35
CK-MB at 12h(IU/L)	27.13+1.85	28.05+3.04	.135
CK-MB at 24h(IU/L)	27.63+1.7	27.85+2.2	.63
CK-MB at 48h(IU/L)	22.95+2.76	23.27+3.6	.69
First postoperative day serum creatinine (mg/dl)	1.29+0.395	1.33+0.57	.77
Postoperative EF (%)	50.78+8.72	50.57+8.38	.92
Low CO state	6.25%(N = 2)	5.71%(n = 2)	.93
In-hospital mortality	3.13%(n = 1)	0%	.29
One-year mortality	0%	2.85%(n = 1)	.33
Limb ischemia	0%	0%	
Neurapaxia of right limb	0%	0%	

DISCUSSION

Reperfusion of transiently ischemic myocardium results in myocardial injury. Twenty-five percent to 45% patients with early postoperative death after CABG showed evidence of ischemia/reperfusion injury [Weman 2000]. Despite the advancement in surgical approach, 10% of patients undergoing CABG develop myocardial infarction, LV dysfunction, heart failure, or death [Mentzer 2008]. Various biological markers (CK-MB level, Troponin T or Troponin I) of myocardial injury are used in different experimental and clinical studies as a as surrogate marker of myocardial injury following open heart surgery. Quality of myocardial protection and resultant degree of myocardial injury is quantified based on the postoperative rise in CK-MB levels. Higher levels of postoperative CK-MB are associated with higher six-month mortality after CABG [Klatte 2001]. Safety of RIPC, reduced level of inflammatory mediator release (IL-1, IL10, and TNF-alpha) and reduced level of cardiac enzyme release in the postoperative period are shown by Zhou and colleagues [Zhou 2010]. Thielmann et al showed that release of TnI in patients with RIPC is lower as compared with a control group with significantly reduced mortality after 1.54 years follow up [Thielmann 2013]. Ali and colleagues showed that application of RIPC by transient limb ischemia in patients undergoing on-pump CABG significantly reduced postoperative CK-MB levels [Ali 2010]. Study by Lomivorotov and colleagues shows postoperative hemodynamics are better in CABG patients, but CK-MB levels are not affected by phenomena of RIPC [Lomivorotov 2012]. Hong et al conducted study where they showed that a statistically insignificant release of TnI was found between RIPC and a control group undergoing off-pump CABG [Hong 2012]. This complex situation and conflicting results of quantitative measurement of myocardial injury after CABG with or without RICP produce a question mark.

Study conducted at University Hospital Birmingham NHS showed that RIPC in on-pump CABG patients does not show any statistical difference in release of TnT, post-aortic cross-clamp ventricular fibrillation, de novo LBBB, de novo Q-waves in ECG, hemodynamics superiority, demand for IABP or inotropic support, treated postoperative atrial fibrillation, postoperative ejection fraction, and postoperative serum creatinine versus placebo group [Rahman 2010]. RIPC does not reduce the level of highly sensitive troponin T (hsTNT) levels, acute kidney injury, and inotropic demand in high risk cardiac surgery patients [Young 2012]. A meta-analysis by Daniel Brevoord and associates showed that RIPC does not improve mortality, major adverse cardiovascular event, length of hospital stay, and ICU-stay in patients undergoing open heart surgery [Brevoord 2012]. While clinical benefit of RIPC has not been well-established after cardiac surgery, RIPC is a safe adjuvant to myocardial protection [Marczak 2012]. Further studies are needed to establish the role of RIPC in myocardial protection in open heart surgery.

CONCLUSION

RIPC is safe technique, but it does not have additional clinical benefit after on-pump CABG surgery in presence of standard myocardial protective strategy.

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