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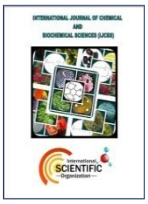

The short outcome of patients undergoing off-pump CABG using remote versus regional ischemic preconditioning

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Abstract

Ischemic preconditioning (IPC) is defined as the protection of the myocardium by inducing a short ischemic period before a subsequent, more extended period of ischemia**.** To assess the short outcome of patients undergoing off-pump CABG using remote versus regional ischemic preconditioning & its effect on myocardial perfusion injury according to the cardiac enzymes & cardiac contractility by Echocardiogram. This is a prospective comparative study in which comparison of the short outcome of patients undergoing off-pump CABG between those who used remote and those using regional ischemic preconditioning (PC) and compare its effect on the myocardial perfusion injury according to both the cardiac enzymes and the cardiac contractility by Echocardiogram. The study involved 100 patients classified into two equal groups; group (A) used regional ischemic PC, and group (B) used remote ischemic PC. There were 32 males (64%) and 18 females (36%) in group (A) and 35 males (70%) and 15 females (30%) in group (B). Regarding postoperative cardiac enzymes serials of cardiac enzymes had been done in 12,24 and 72 hours postoperative and showed a significant decrease in both groups subsequently and showed nonsignificant difference (p >0.05) between both groups. However, both groups of the study showed significant reduction in serum Troponin levels as Hs-TnI in both groups postoperative values at 12 hours: were group (A) 0.365 group B 0.363, 24 hours: group (A)0.255 group B 0.253, 72 hours group (A)0.038, group (B)0.036 & at 120 hrs group (A) decreased to 0.026 & group B also decreased to 0.024. Our study in comparison with other studies, showed a great outcome in myocardial contractility and a low incidence of cardiac reperfusion injury for those being applied ischemic preconditioning. Regarding remote and regional ischemic preconditioning, there were no significant differences in myocardial protection, reperfusion injury or postoperative outcome, however remote precondition is technically safer to be applied than regional coronary occlusion.

Keywords: CABG, off-pump, regional, remote, preconditioning.

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1. Introduction

Ischemic preconditioning (IPC), defined as protection of the myocardium by inducing a short ischemic period before a subsequent longer period of ischemia, was first described by Murry and colleagues (Murry et al., 1986). Since then, the phenomenon has been confirmed in numerous animal studies, but despite intensive research, its basic cellular mechanisms are not yet fully understood (Yellon et al., 1998). Peri-infarction angina in humans has been found to act like IPC because it preserves left ventricular function, even without collateral coronary artery circulation (Nakagawa et al., 1995). Coronary artery angioplasty has been a popular model in studying IPC in human subjects, but the results are conflicting (Eltchaninoff et al., 1997).

In coronary artery bypass grafting (CABG) performed with cardiopulmonary bypass, IPC has been found to be effective during intermittent aortic cross clamping (Alkhulaifi et al., 1994) or with normothermic or mild hypothermic cardioplegia but not with cold cardioplegia (Cremer et al., 1997), although several conflicting results also exist (Kaukoranta et al., 1997), IPC alone had similar protective effects as cardioplegia (Kolocassides et al., 1994) and also ensured optimal myocardial protection when the delivery of cardioplegic solution was impaired (Galiñanes et al., 1995). In CABG without cardiopulmonary bypass, the coronary artery to be grafted is usually occluded during the suturing of the distal anastomosis, and the ischemic periods are longer than those in coronary angioplasty, thus offering a model to study the effects of IPC in human subjects.

A more intriguing form of ischemic pre-conditioning with potentially greater clinical significance is remote ischemic preconditioning “rIPC” i.e., transient tissue ischemia at a distance may confer subsequent protection of an organ subjected to potentially lethal ischemia (Loukogeorgakis et al., 2005). Despite substantial improvements in myocardial preservation strategies, coronary artery bypass grafting (CABG) is still associated with severe complications. It has been reported that remote ischaemic preconditioning (RIPC) reduces reperfusion injury in people undergoing cardiac surgery and improves clinical outcome (Benstoem et al., 2017).

2. Aim of the work

The aim of our study is to assess the short outcome of patients undergoing off-pump CABG using remote versus regional ischemic preconditioning & its effect on myocardial perfusion injury according to the cardiac enzymes & cardiac contractility by Echocardiogram.

3. Patients and methods

3.1. Study design

3.1.1. Type and sitting of the study

This is a prospective clinical comparative study in which comparison of the short outcomes of patients undergoing off-pump coronary artery bypass grafting (OPCABG) between those who used remote and those used regional ischemic preconditioning and compare its effect on the myocardial perfusion injury according to both the cardiac enzymes and the cardiac contractility by Echocardiogram. The study involved one-hundred patients undergoing off-pump CABG. They were collected and operated at the cardiothoracic surgery department, Misr University for science & technology and the cardiothoracic surgery department, Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University at the period from January 2021 to February 2023.

3.1.2. Research questions

In this thesis we try to answer the question: Is there a difference between remote and regional ischemic preconditioning in patients undergoing off-pump CABG?

3.1.3. Subjects and Sampling

One hundred patients undergoing off-pump CABG represented the target population of this study. They were divided into two equal groups each of fifty patients. They were matching our inclusion criteria.

3.1.3.1. Grouping

3.1.3.1.1 Group (A)

50 patients who undergoing off-pump CABG and used regional ischemic preconditioning.

3.1.3.1.2 Group (B)

50 patients who undergoing off-pump CABG and used remote ischemic preconditioning.

3.1.3.2. Inclusion criteria

Patients age > 30 years of age. Patients undergoing off-pump CABG. Patients with intact pulse in all limbs.

3.1.3.3. Exclusion criteria

Low age patients <30 years. Valve heart surgery. Using cardiopulmonary bypass. Any other cardiac problems rather than coronary artery disease. Internal fixation of any limb. Lower limb ischemia. A-V fistula. Patients who refuse to participate in the study.

4. Methodology

Complete assessment was done for each patient including;

4.1. Full history taking

Personal history: name, age, sex, residence and occupation. Clinical history: history of claudication LL pain, history of renal dialysis or A-V fistula formation, previous limb fracture and internal fixation, Previous CABG, Previous valve replacement, myocardial infarction (MI), Previous PCI, history of blood diseases, Current tobacco smoking and history of COPD. Medical history: previous medical illness, chest pain, comorbidities. History of previous cardiac medication. History of PCI: PCI initially successful then failed or PCI initially failed.

4.2. Patients Evaluation

Electrocardiogram (ECG): to reveal old or new ischemia of infarction, heart dilatation or hypertrophy & arrhythmias. Echocardiogram: to reveal heart contractility, segmental wall motion and valves lesions. Finding of angiogram vessel anatomy suggests CABG. Carotid and lower limb arterial duplex. Determination of emergent cases or elective cases. Chest computed tomography (CT) for determination of aortic calcification.

4.3. Laboratory reports

Determination of Complete blood count (CBC). Coagulation profile and international normalized ratio (INR). Bleeding profile. Liver and kidney function tests. Cardiac Enzymes: creatinine kinase (CK), CK-MB, highly sensitive troponin (Hs-Tn). Blood glucose tests: fasting and postprandial, glycosylated hemoglobin (HBA1c). Highly sensitive cardiac Troponin T & I (cTnT & cTnI): for the test blood samples were taken at 12, 24, 72, and 120 hours. Lipid profile: Total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), serum triglyceride (TG). Virology: hepatic markers for HCV and HBV.

4.4. Preoperative and operative data

Time for hospital admission to CABG. Duration of surgery. Number of vessel grafts. Time of distal anastomosis of each graft. In regional ischemic preconditioning group: two cycles of 2 minutes left anterior descending artery (LAD) occlusion followed by 3 minutes of reperfusion before the first coronary artery anastomosis. Ischemic remote preconditioning: elicited with 4 cycles of 5 minutes of ischemia by cuff inflation >200 mmHg and 5 minutes of reperfusion of the upper limb before and after anastomosis.
Intraoperative complications were recorded. Cardiac contractility post anastomosis. Arrhythmias during the ischemia or the reperfusion.

4.5. Postoperative data

Signs of low cardiac output. Signs of limb ischemia. Pharmacological inotropes. Intra-aortic balloon (IAP). Echocardiogram: to assess the contractility and segmental wall motion. Electrocardiogram: to assess new ischemia, infarction and arrhythmias. Cardiac enzymes:

highly sensitive troponin T throughout 72 hours. Duration of ICU and hospital stay.

4.6. Study Outcomes

4.6.1. Primary outcome

Cardiac contractility by echocardiogram and cardiac enzymes postoperative to assess myocardial reperfusion injury in both groups. Cardiac troponin T (cTnT, ng/L) and I (cTnI, ng/L) at 48 hours, 72 hours, and as area under the curve (AUC) 72 hours (μg/L) after surgery. Presence of hospital mortality (death that occurs before hospital discharge).

4.6.2. Secondary outcome

Non-fatal myocardial infarction after 30 days. Any new stroke after 30 days. Acute renal failure after 30 days. Length of stay on the intensive care unit (days) and total hospital stays. Any complications and adverse effects related to ischemic preconditioning, as reported by trial authors.

4.7. Administrative Design

4.7.1. Ethical considerations

The study was conducted after approval of the protocol by the Local Research Committee & the Studies Committee as well as the Research Ethics Committee. An informed written consent was obtained from all patients that contain the following: The aim, procedures and duration of the study explained in a simple way. The patients have the right to refuse participation without affecting the medical care expected to be offered to the patient. The patients have the right to withdraw from the study at any time without any penalty and without giving reasons. Confidentiality of data and results of all study population was preserved by ensuring anonymity of data and minimal access to data by research team only: Access to master sheet is limited. Master sheet is stored separately from the rest of the data. Contact lists are destroyed when no longer required for the research. Files containing electronic data are password protected and encrypted (at least during transfer/transport). Research data is stored securely in locked cabinets or rooms. Electronic data are stored in password protected computers. Files containing electronic data are closed when computers are left un-attended. Consents are stored securely in locked cabinets or rooms, separately from the research data.

5. Statistical Data Analysis

Data were analyzed using the statistical package SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). A normal distribution of variables was assessed using the Kolmogorov–Smirnov test. Data were described using the suitable measures for central tendency and dispersion as well as percentage as indicated. T-tests are used for continuous variables and expressed as means ± SD. While Chi square tests are used for categorical variables. Pearson correlation and multivariate linear regression test were used to assess the correlation between different variables. All statistical tests were 2-tailed, the probability of error equal to or less than 0.05 ($p \leq 0.05$) was considered significant.

6. Results & discussion

6.1. Preoperative data

Age of group (A) ranged from 37 to 66 years with mean ± SD of 54.38 ± 7.02 years and the ages of group (B) was ranged from 36 to 69 years with mean of 54.84 ± 8.47 years. Gender; They were 32 males (64%) and 18 females (36%) in group (A) and 35 males (70%) and 15 females (30%) in group (B). Both groups were age and sex matched as p >0.05, i.e., non-significant. Preoperative BMI of group (A) ranged from 22 to 37 Kg/m^2 and BMI of group (B) ranged from 22 to 31.5 Kg/m^2. BSA of group (A) ranged from 1.5 to 2.3 m^2 and BSA of group (B) ranged from 1.2 to 2.3 m^2. So, were BMI and BSA were statistically non-significant difference (P >0.05) in comparison between the two groups. Similar to our study, Wang et al. (2019) demonstrated the characteristics of patients in the two groups were comparable regarding their gender, age and body weight. Also, Gurung and Parajuli (2021) had 47 patients classified into two groups (23 RICP and 24 controls). They were 17 males (73.9%) and 6 females (26.1%) in RICP group, and 17 males (70.8%) and 7 females (29.2%) in control group. The mean age was 64 in both groups. The mean BMI was 23.95 ±2.89 and 23.60 ±2.72 Kg/m^2 in RIPC group and control group, respectively. All these parameters were statistically insignificant (p >0.05) in comparison between the two groups. Preoperative clinical signs of blood pressure and heart rate were group(A): mean bp 140/70 ± 9.58 mmHg and the heart rate 69 ± 8.14 bpm . Group(B) mean bp 140/80 ±10 mmHg and the heart rate 69.1 ± 9.24 bpm statistically non-significant difference (P >0.05) in comparison between the two studied groups.

Gurung and Parajuli (2021) had similar blood pressure in both groups and they had 15 patients (65.2% & 65.5%) with hypertension in both groups with statistically insignificant difference (p >0.05). Regarding echocardiogram, we focused on the left ventricle dimensions and contractility and if there are segmental wall motion abnormalities and valvular lesions had been found, comparison is made between both groups. Comparison between the two groups as regard baseline echo findings showed in group (A): the mean of LVEDD:4.6 cm (±0.046 SD), LVESD:3.3 cm (±0.018 SD), EF: 53% (±5.95 SD) and SWMAs: 48% (24 cases) while in group (B): The mean of LVEDD:4.6 cm (±0.632 SD), LVESD:3.3 cm (±0.016 SD), EF: 63% (±4.97 SD) and SWMAs: 46% (23 cases). Statistically non-significant difference (p >0.05) in all echocardiographic parameters. Gurung and Parajuli (2021) had similar echocardiographic parameters in both groups. They found that LVEF >55% in 20 cases (86.96%) and 20 cases (83.33%) in groups (1) & (2), respectively. LVEF 35-55% in 3 cases (13%) and 4 cases (16.7%) in groups (1) & (2), respectively. They all showed statistically insignificant difference (p >0.05). In ECG we focused on old and new ischemic changes and if there was bundle branch block preoperatively. Comparison between the two groups as regard preoperative ECG findings showed non-significant difference (p >0.05) in all ECG parameters between both groups, however ST segment depression was slightly more in remote PC group preoperative. 15 cases in this group have ST-segment depression more than 1 ms, while in group A were 11 cases. ST-segment elevation in group(A) 22 cases while in group (B) were 21 cases. LBBB: group (A) 21 cases, group (B) 22 cases.

Abnormal Q-wave: group (A) 35 cases, group (B) 36 cases. There no clear studies showed ECG data preoperative. Regarding to coronary angiography for both groups, we mentioned the vessels which have stenosis and need revascularization both groups. Comparison between the two groups as regard stenosed vessels showed in group (A): 35% of the cases have left main coronary stenosis, LAD 100%, RCA 65% and LCx 70%. While in group (B): 30% of cases have left main coronary stenosis, LAD 100%, RCA 70% and LCx 75%. Statistically non-significant difference (p >0.05) in all vessels. Comparison of cardiac enzymes (CK, CK-MB, Troponin-I) between the two groups showed in group (A) CK were ranged 87-351 u/l, CK-MB ranged 3.1-5.9 ng/ml & Troponin I 0.008-0.015 ng/ml. While in group (B) CK were ranged 72-344 u/l, CK-MB ranged 3.2-5.8 ng/ml & Troponin I 0.009-0.013 ng/ml. There was insignificant difference (p >0.05) in all patients. Similar results obtained by Gurung and Parajuli (2021) as they found preoperative cardiac enzymes (cTnI, CK, CK-Mb, and NTproBNP) showed statistically insignificant difference in comparison between the two groups.

6.2. Intraoperative data

Regarding the graft types and number used intraoperatively: Internal thoracic artery (ITA) was the most vessel used in our operation in regional and remote groups whether alone, (In group A only one case while no cases in group B that used a single graft), ITA with saphenous vein (group A 76% of cases, group B 45%) or with SV and radial artery (group A22%, group B 46%), respectively. It was observed that 2 vessels were the most common used 48% of cases in each group , followed by 3 vessels 46% in group A & 32% in group B, then 4 vessels 4% in group A&20% in group B and the least was one vessel only 2% in group A & no cases in group B. Comparison between the two groups as regard number and type of vessels used showed statistically significant difference (p <0.05), except 2 vessels were similar in both groups (p >0.05). In agreement with our results, Gurung and Parajuli (2021) study showed that most of their grafts were 2 vessel grafts in 13 cases (56.5%) and 8 cases (33.3%) in group (1) & (2), respectively, followed by 3-vessel in 7 cases (30.4%) and 11 cases (45.8%), respectively, then one vessel (4.2%) in the control group.

6.2.1 Times

Estimated time of the operation was slightly longer (241.2 ± 45.8 min) in remote PC than regional one (239.6 ± 45.1 min), but it was insignificant (p >0.05) and time of anastomosis were similar in both groups (107.3 ± 23.6 and 108.9 ± 26.2) in regional and remote groups, respectively, with statistically insignificant difference (p >0.05). The time of anastomosis is calculated proximally and distally in both groups. In Gurung and Parajuli (2021) study, the operation times were 279.57 ±51.24 min and 285 ±46.7 min in remote and reginal groups, respectively. They showed statistically insignificant difference (p >0.05). Intraoperative complications There were certain intraoperative complications in both groups: when we applied a preconditioning there were certain complications intraoperative in form of vascular & myocardial injury, pump failure and arrhythmias.

Vascular and myocardial injuries in the form of tear of the vessel adjacent myocardium during the dissection on the vessel or applying regional preconditioning, it happened in 3 patients(6%) in group (A) while in group (B) there was no vascular or myocardial injuries. Arrhythmias in 3 patients (6%) of group A while group B there was one patient only (2%) when the preconditioning going on in patients of both groups. Pump failure and low cardiac output in one patient (2%) of group (A)only had been noticed, that’s why high doses of inotropes and intra-aortic balloon pump (IABP) were needed and didn’t happen in group (B).
It was observed that regional group had more complications (98%) than remote one (62%). The most common complications were low cardiac output and local vascular injury. Regarding Tantawy and Mosa (2020) the study was done on 40 patients showed intraoperative complications in form of hemodynamic instability in 3 patients (7.5%) due to stabilizer compression and heart manipulation that cause low cardiac output and some arrhythmias in form of atrial fibrillation in 6 patients (15%).

Khan et al. (2017) meta-analysis study was conducted on 27,623 patients through 10 years and found that intraoperative atrial fibrillation happened in 31% of the patients. Puskas et al. (2003) the study was conducted on 98 patients and atrial fibrillation had happened in (16.3%) of them while local vessel occlusion applied. Rahman et al.2010) the study was conducted to 80 patients undergone off-pump CABG with remote preconditioning and intraoperative complications were in form of atrial fibrillation in 35% of the patients and hemodynamics instability and IABP inserted in 6% of the patients.. From the comparison between our study and other studies, the obvious difference in our study was mechanical vascular and myocardial injury had happened in one case in regional preconditioning group but it was managed safely and the operation done smoothly after that.

6.3. Postoperative data

Postoperative hemodynamics in form of blood pressure. heart rate & rhythm in both groups in ICU postoperative. Systolic blood pressure (139.7 ± 10.8 mmHg in group A & 141.5 ± 12.3 mmHg in group B), Diastolic blood pressure (71.7 ± 9.84 mmHg in group A & 75.5 ± 10.3 mmHg in group B), heart rate (58.9 ± 8.45 bpm in group A& 59.1 ± 9.27 bpm in group B). inotropes: 50% of group (A) were on low dose of adrenaline nearly 50 ng/kg/hr in 1st day postoperative and withdrawn gradually except only one patient was on high doses of adrenaline, noradrenaline and IABP and this withdrawn gradually also after the stability has been done, also 46% of group B were on a similar dose of adrenaline 1st day postoperative and gradually withdrawn and there no patient in group B was on IABP or on high doses of inotropes. Patients in both groups postoperative showed hemodynamics stability and they were statistically insignificant in comparison between regional and remote groups, respectively. In comparison with Rahman et al. (2010) study in which applied remote ischemic preconditioning on 80 patients and 6 of them IABP has been insterted and 50% of cases were on low dose of inotropes. Regard postoperative cardiac enzymes serials of cardiac enzymes had been done in 12,24 and 72 hours postoperative and showed a significant decrease in both groups subsequently and showed nonsignificant difference (p >0.05) between both groups. However, both groups of the study showed significant reduction in serum Troponin levels as Hs-TnI in both groups postoperative values at 12 hours: were group (A) 0.365 group B 0.363, 24 hours: group (A)0.255 group B 0.253, 72 hours group (A)0.038, group (B)0.036 & at 120 hrs group (A) decreased to 0.026 & group B also decreased to 0.024.

In agreement with our results, Wang et al. (2019) found that plasma levels of cTnT in two groups were comparable. before the surgery. After the surgery, the cTnT level in both groups were increased. RIPC treatment significantly reduced the cTnT levels after 120 h (control vs. RIPC: 0.273 ± 0.397 ng/ml vs. 0.108 ± 0.110 ng/ml, $p < 0.05$). Our study had similar results to Gurung and Parajuli (2021) who demonstrated that RIPC, induced by brief ischemia and reperfusion of both upper and lower limbs with standard blood-pressure cuffs, did not cause a significant difference in the postoperative release of cTnI, CKMB, and NTproBNP in patients undergoing elective OPCABG surgery. This result was comparable to few previous studies that also reported no significant reduction in the release of cardiac enzymes with RIPC after cardiac surgery (Hong et al., 2010). In a subsequent clinical trial, RIPC by cycles of ischemia/ reperfusion reduced the extent of myocardial injury measured by troponin release during elective coronary artery bypass surgery (Hausenloy et al., 2007). In their study of cardiac surgery, three cycles of 5-min ischemia and 5-min reperfusion of the upper limb using a pressure cuff inflated to 200 mmHg reduced troponin-T release during 48 h after coronary artery bypass graft (CABG) surgery. Several subsequent studies have reported favorable outcomes following this landmark trial. Similarly, RIPC protocol also reduced the postoperative release of cardiac troponin-I within 72 h after CABG and reduced all-cause mortality in the 1.5 years following surgery (Thielmann et al., 2013). Two cycles of simultaneous upper and lower limb ischemia/reperfusion reduced 72-h postoperative troponin-T concentrations in patients undergoing CABG, as compared to the control group (Candilio et al., 2015). Moreover, RIPC ameliorated sinus rhythm restoration up to 1 year after surgery and reduced postoperative markers of systemic inflammation in patients undergoing Cox maze radiofrequency ablation with concomitant mitral valve surgery (Jiang et al., 2019).

However, not all studies evaluating RIPC during cardiac surgery demonstrated favorable results and a reduction in cardiac biomarkers. Hong et al. (2010) did not observe any reduction in the postoperative release of troponin-I during 72 h following the application of four cycles of RIPC in patients undergoing off-pump CABG. In patients with concentric myocardial hypertrophy undergoing aortic valve replacement, three cycles of upper limb RIPC did not affect the 24-h area under the curve for creatine kinase-myocardial band or troponin-T levels following the surgery (Song et al., 2017). Also, in contrast Cabrera-Fuentes et al. (2015) stated that a causal relationship was not proven because the troponin level was not reduced by conditioning.

Although some inconsistent results have been presented, a recent meta-analysis reported the protective effects of RIPC, as measured by cardiac biomarkers. After pooling the results of 30 trials of CABG or valve surgery, RIPC was found to reduce postoperative troponin release compared to the control arm (no ischemic preconditioning) (Xie et al., 2018). Creatine kinase is normally elevated postoperative and return to the normal level within 72 hours in both groups. Comparison between the two groups as regard pre or postoperative CK showed insignificant difference (p >0.05), while intergroup study showed highly significant CK elevation (p <0.001) between preoperative and postoperative CK in both groups. Comparison between the two groups as regard pre and postoperative CK-MB showed insignificant difference (p >0.05), while intergroup study showed significant CK-MB elevation (p <0.05) between preoperative and postoperative values in both groups. The same results obtained by Cho and Kim (2019) study they reported significant elevation of creatine kinase and CK-MB just postoperative however, they return to normal with few days after using RIPC. It has no clinical benefit. It is reported that RIPC reduces the release of myocardial enzymes after the cardiac surgery, but without clinical benefit (Ahmad et al., 2014; Benstoem et al., 2017). In the Wang et al. (2019) study, patients in control group had elevated levels of cTnT indicating that the surgery indeed induces myocardial damage. RIPC treatment reduced oxidative stress, decreased production of inflammatory cytokines, downregulated protein expression of myocardial injury makers, suggesting that RIPC protects surgery-induced damage in cardiac myocytes.

Also, in agreement with Laurikka et al. (2002) who applied regional ischemic preconditioning on 32 patients and the results showed a significant reduction in CTnI postoperative more marked than controlled group and a smaller CK-MB release after surgery (not significant).

According to our study in comparable with other studies, it showed a great outcome in myocardial contractility and low incidence of cardiac reperfusion injury for those being applied ischemic preconditioning. Regarding to remote and regional ischemic preconditioning, there were no significant difference in myocardial protection, reperfusion injury or postoperative outcome, however remote precondition is technically safer to be applied than regional coronary occlusion. In the current study, echo doppler done to both groups in 3rd or 4th day postoperatively to assess the ventricular function and the segmental wall motion abnormalities and comparison between the two groups was done and showed in group (A): EF: 50% and SWMAs: 24% (12 cases) while in group (B): EF: 58% and SWMAs: 20% (10 cases). Statistically non-significant difference (p >0.05) in all echocardiographic parameters.

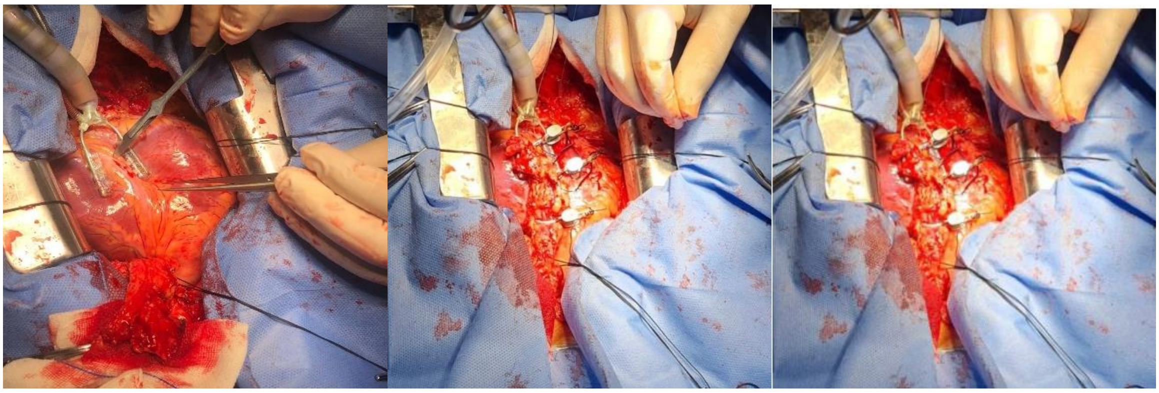

Figure (1): Regional ischemic preconditioning (LIMA to LAD).

Figure (2): Remote preconditioning.

Table (1): Demographic data of the two studied groups.

	Group (A)		Group (B)		Significance	
Gender	**No.**	**%**	**No.**	**%**	**χ^2**	**P**
Males	32	64.0	35	70.0	0.255	0.246
Females	18	36.0	15	30.0	0.849	0.122
Total	50	100	50	100		
Age (years)					**t**	**P**
Range	37 – 66		36 – 69			
Mean ± SD	54.38 ± 7.02		54.84 ± 8.47		0.058	0.847
BMI (kg/m^2)						
Range	22 – 37		22 – 31.5			
Mean ± SD	28.06 ± 4.18		26.15 ± 2.26		0.224	0.517
BSA (m^2)						
Range	1.5 – 2.3		1.2 – 2.3			
Mean ± SD	1.82 ± 0.21		1.71 ± 0.26		0.451	0.074

χ^2 = Chi square, t: unpaired t-test, SD: standard deviation, p>0.05= insignificant, BMI: body mass index, BSA: body surface area.

Table (2): Baseline clinical signs of the two studied groups.

Groups / Item	Regional PC (Group A)	Remote PC (Group B)	Significance	
			t	**P**
SBP (mmHg)				
• Range	126 – 162	102 – 170		
• Mean ± SD	141.56 ± 9.58	139.5 ± 17.61	0.132	0.685
DBP (mmHg)				
• Range	58 – 84	67 – 91		
• Mean ± SD	70.56 ± 7.38	79.94 ± 5.39	0.521	0.062
Heart rate (bpm)				
• Range	59 – 85	61 – 88		
• Mean ± SD	68.5 ± 8.14	69.1 ± 9.24	0.044	0.879

t: unpaired t-test, P >0.05 = non-significant, SBP: systolic blood pressure, DBP: diastolic blood pressure, bpm: beat per minute.

Table (3): Preoperative echocardiographic parameters of the two studied groups

Echocardiographic parameters	Regional PC		Remote PC		Significance	
	Mean	± SD	Mean	± SD	t	P
LVEDD (cm)	4.643	0.046	4.667	0.632	0.003	0.937
LVESD (cm)	3.292	0.018	3.311	0.016	0.048	0.764
EF (%)	53.08	5.952	63.02	4.971	0.341	0.111
LAD (cm)	2.628	0.254	3.337	0.579	0.559	0.052
	No.	%	No.	%	χ^2	P
SWMAs	24	48.0	23	46.0	0.0913	0.578

t: unpaired t-test, P >0.05 = statistically insignificant, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, EF: ejection fraction, LAD: left atrial diameter, SWMAs: segmental wall motion abnormalities.

Table (4): Comparison between preoperative regional and remote PC groups as regard ECG findings

ECG findings	Regional PC		Remote PC		Significance	
	Mean	± SD	Mean	± SD	t	P
P wave (ms)	109.3	8.14	110.7	6.39	0.001	0.972
PR interval (ms)	155.8	23.98	156.9	21.02	0.001	0.975
QRS (ms)	92.06	6.52	92.10	5.85	0.000	0.998
QTc (sec)	0.423	0.046	0.405	0.036	0.041	0.794
ST-segment	No.	%	No.	%	χ^2	P
Isoelectric	17	34	14	28	0.445	0.21
Slight deep >1 ms	11	22	15	30	1.603	0.041*
Elevated >1 ms	22	44	21	42	0.002	0.948
RBBB	18	36	16	32	1.265	0.078
LBBB	21	42	22	44	0.698	0.163
Abnormal T-wave	39	78	38	76	0.12	0.279
Abnormal Q-wave	35	70	36	72	0.128	0.274

t: unpaired t-test, *P <0.05 = statistically significant.

Table (5): Coronary angiography stenosis percentage in the two studied groups

Stenosis (%) in Mean ± SD	Regional PC (Group A)	Remote PC (Group B)	Significance	
			t	P
RCA	65.68 ± 8.61	76.92 ± 6.76	0.367	0.123
LCX	69.62 ± 7.87	75.64 ± 8.70	0.264	0.254
LAD	100	100	0.000	1.000
PDA	72.43 ± 8.51	73.24 ± 7.45	0.037	0.827
LMA	35 ± 5.42	30 ± 6.93	0.061	0.744

t: unpaired t-test, P >0.05 = non-significant., RCA: right coronary artery, LCX: left circumflex artery, LAD: left anterior descending artery, PDA: posterior descending artery, LMA: left (Main) artery.

Table (6): Preoperative cardiac enzymes of the two studied groups

Preoperative cardiac enzymes	Regional PC (Group A)	Remote PC (Group B)	Significance	
			t	P
Creatinine kinase				
• Range (U/L)	87 – 351	72 – 344		
• Mean ± SD	208.2 ± 77.17	201.7 ± 67.15	0.010	0.899
Ck-MB (ng/ml)				
• Range	3.1 – 5.9	3.2 – 5.8		
• Mean ± SD	4.504 ± 0.87	4.474 ± 0.81	0.064	0.681
Hs-TnI (ng/mL)	0.015 ± 0.008	0.013 ± 0.009	0.025	0.159

Table (7): Graft number and type in the two studied groups

Graft number	Regional PC		Remote PC		Significance	
	No.	%	No.	%	χ^2	P
1 vessel	1	2	0	0	1.913	0.012*
2 vessels	24	48	24	48	0.000	1.000
3 vessels	23	46	16	32	2.518	0.008*
4 vessels	2	4	10	20	21.36	0.000*
Graft type						
ITA	1	2	0	0	1.913	0.012*
ITA + SV	38	76	27	54	1.589	0.043*
ITA+RA+SV	11	22	23	46	5.967	0.001*
Total	50	100	50	100		

χ^2: Chi square test, P >0.05: non-significant, *P <0.05: significant, ITA: Internal thoracic (mammary) artery. RA: Radial artery, SV: saphenous vein.

Table (8): Operative times of the two studied groups

Operative parameters	Regional PC		Remote PC		Significance	
	Mean	± SD	Mean	± SD	t	P
Anastomosis time (m)	107.3	23.6	108.9	26.2	0.001	0.998
Operation time (m)	239.6	45.1	241.2	45.8	0.022	0.897

t: unpaired t-test, *P <0.05 = statistically significant.

Table (9): Intraoperative complications in regional and remote PC groups

Complications	Regional PC		Remote PC	
	No.	%	No.	%
Vascular injury	3	6	0	0
High surgical draining	4	8	2	4
Pump failure	1	2	0	0
Low cardiac output	12	24	5	10
Arrhythmias	3	6	1	2
IABP need	1	2	0	0
Positive inotropes need	25	50	23	46
Total	49	98	31	62

Table (10): Postoperative hemodynamics of the two studied groups.

Groups / Item	Regional PC (Group A)	Remote PC (Group B)	Significance	
			t	P
SBP (mmHg)				
• Range	121 – 155	112 – 161		
• Mean ± SD	139.7 ± 10.8	141.5 ± 12.3	0.061	0.699
DBP (mmHg)				
• Range	61 – 86	63 – 92		
• Mean ± SD	71.7 ± 9.84	75.5 ± 10.3	0.097	0.528
Heart rate (bpm)				
• Range	53 – 65	54 – 68		
• Mean ± SD	58.9 ± 8.45	59.1 ± 9.27	0.019	0.891

t: unpaired t-test, P >0.05 = non-significant, SBP: systolic blood pressure, DBP: diastolic blood pressure, bpm: beat per minute.

Table (11): Postoperative outcome between regional and remote PC groups

Outcome	Regional PC		Remote PC		Significance	
	No.	%	No.	%	χ^2	P
Chest pain	3	6	2	4	0.894	0.053
Positive inotropes	25	50	23	46	0.271	0.218
IABP	1	2	0	0	**0.539**	**0.895**
MV (hours)	20.64	1.26	20.94	1.63	0.001	0.995

χ^2: Chi square, t: unpaired t-test, P >0.05 = statistically non-significant, MV: mechanical ventilation time.

Table (12): Postoperative complications in regional and remote PC groups

Complications	Regional PC		Remote PC	
	No.	%	No.	%
Low urine output	7	14	8	16
Arrhythmias	3	6	1	2
Wound infection	1	2	0	0
Chest infection	9	18	5	10
Prolonged MV	8	16	6	12
30-day mortality	2	4	1	2
Total	30	62	21	42

MV: mechanical ventilation.

Table (13): Postoperative cardiac enzymes of the two studied groups

Cardiac enzymes	Regional PC (Group A)	Remote PC (Group B)	Significance	
			t	P
CK (U/L)				
• Range	176 – 443	99 – 371		
• Mean ± SD	300.2 ± 75.92	298.5 ± 73.11	0.005	0.981
CK-MB (ng/mL)				
• Range	4.01 – 6.81	4.0 – 6.6		
• Mean ± SD	5.414 ± 0.91	5.274 ± 0.84	0.085	0.481
Hs-TnI (ng/mL)				
12 hours	0.365 ± 0.44	0.363 ± 0.043	0.059	0.694
24 hours	0.255±0.01	0.253±0.11	0.112	0.927
72 hours	0.038 ± 0.009	0.036 ± 0.10	0.008	0.198
120 hours	0.026 ± 0.009	0.024 ± 0.009	0.009	0.148

t: unpaired t-test, *P <0.05 = statistically significant.

Table (14): Postoperative echo Doppler parameters of the two studied groups

Echocardiographic parameters	Regional PC		Remote PC		Significance	
	Mean	± SD	Mean	± SD	t	P
LVEDD (cm)	4.592	0.121	4.611	0.235	0.002	0.954
LVESD (cm)	3.286	0.086	3.291	0.118	0.001	0.978
EF (%)	55	6.122	58	5.979	0.498	0.091
LAD (cm)	1.598	0.223	2.039	0.191	0.516	0.089
	No.	%	No.	%	χ^2	P
SWMAs	12	24.0	10	20.0	0.001	0.179

t: unpaired t-test, P >0.05 = statistically insignificant, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, EF: ejection fraction, LAD: left atrial diameter, SWMAs: segmental wall motion abnormalities.

Table (15): Comparison between postoperative regional and remote PC regarding ECG findings

ECG findings	Regional PC		Remote PC		Significance	
	Mean	**± SD**	**Mean**	**± SD**	**t**	**P**
P wave (ms)	97.28	7.54	99.68	6.12	0.002	0.933
PR interval (ms)	141.78	20.19	133.9	18.34	0.058	0.725
QRS (ms)	85.12	5.17	85.1	4.92	0.000	0.991
QTc (sec)	0.333	0.004	0.356	0.028	0.053	0.765
ST-segment	**No.**	**%**	**No.**	**%**	χ^2	**P**
Isoelectric	40	80	40	80	0.000	1.000
Slight deep >1 ms	4	8	1	2	12.85	0.000*
Elevated >1 ms	6	12	9	18	0.867	0.054
RBBB	4	8	3	6	1.271	0.075
LBBB	5	10	5	10	0.000	1.000
Abnormal T-wave	2	4	1	2	1.416	0.054
Abnormal Q-wave	3	6	3	6	0.000	1.000

t: unpaired t-test, *P <0.05 = statistically significant.

Table (16): Comparison of pre and postoperative ECG findings of the regional group.

ECG findings	Preoperative		Postoperative		Significance	
	Mean	**± SD**	**Mean**	**± SD**	**t**	**P**
P wave (ms)	109.3	8.14	97.28	7.54	1.152	0.033*
PR interval (ms)	155.8	23.98	141.78	20.19	1.186	0.027*
QRS (ms)	92.06	6.52	85.12	5.17	1.089	0.049*
QTc (sec)	0.423	0.046	0.333	0.004	1.094	0.047*
ST-segment	**No.**	**%**	**No.**	**%**	χ^2	**P**
Isoelectric	17	34	40	80	8.394	0.000*
Deep >1 ms	11	22	4	8	9.135	0.000*
Elevated >1 ms	22	44	6	12	24.31	0.000*
Abnormal T-wave	39	78	2	4	25.79	0.000*
Abnormal Q-wave	35	70	3	6	24.21	0.000*

t: unpaired t-test, *P <0.05 = statistically significant.

Table (17): Comparison of pre and postoperative ECG findings of remote group.

ECG findings	Preoperative		Postoperative		Significance	
	Mean	**± SD**	**Mean**	**± SD**	**t**	**P**
P wave (ms)	110.7	6.39	99.68	6.12	1.150	0.034*
PR interval (ms)	156.9	21.02	133.9	18.34	1.191	0.023*
QRS (ms)	92.10	5.85	85.1	4.92	1.089	0.049*
QTc (sec)	0.405	0.036	0.356	0.028	1.176	0.049*
ST-segment	**No.**	**%**	**No.**	**%**	χ^2	**P**
Isoelectric	14	28	40	80	9.729	0.000*
Deep >1 ms	15	30	1	2	29.15	0.000*
Elevated >1 ms	21	42	9	18	4.566	0.000*
Abnormal T-wave	38	76	1	2	31.20	0.000*
Abnormal Q-wave	36	72	3	6	30.24	0.000*

t: unpaired t-test, *P <0.05 = statistically significant.

Table (18): Pre and postoperative creatinine kinase of the two studied groups

CK (U/L)	Regional PC (Group A)	Remote PC (Group B)	Significance	
			T	P
Preoperative • Range • Mean ± SD	 87 – 351 208.2 ± 77.17	 72 – 344 201.7 ± 67.15	 0.010	 0.899
Postoperative • Range • Mean ± SD	 176 – 443 300.2 ± 75.92	 99 – 371 298.5 ± 73.11	 0.005	 0.981
t-test#	1.639	1.655		
P value#	0.014*	0.011*		

t: unpaired t-test, *P <0.05 = statistically significant. #: intergroup comparison.

Table (19): Pre and postoperative CK-MB of the two studied groups

CK-MB (ng/mL)	Regional PC (Group A)	Remote PC (Group B)	Significance	
			T	P
Preoperative • Range • Mean ± SD	 3.1 – 5.9 4.504 ± 0.87	 3.2 – 5.8 4.474 ± 0.81	 0.064	 0.681
Postoperative • Range • Mean ± SD	 4.01 – 6.81 5.414 ± 0.91	 4.0 – 6.6 5.274 ± 0.84	 0.085	 0.481
t-test#	0.963	0.947		
P value#	0.046*	0.048*		

t: unpaired t-test, *P <0.05 = statistically significant. #: intergroup comparison.

Table (20): Pre and postoperative highly sensitive cardiac troponin I (Hs-TnI) of the two studied groups

Hs-TnI (ng/mL)	Regional PC		Remote PC		Significance	
	Mean	± SD	Mean	± SD	t	P
Preoperative	0.017	0.009	0.015	0.010	0.028	0.152
12 hours	0.257	0.009	0.255	0.011	0.061	0.696
24 hours	0.367	0.042	0.365	0.043	0.065	0.681
72 hours	0.040	0.009	0.038	0.010	0.008	0.195
120 hours	0.028	0.011	0.026	0.009	0.009	0.187

t: unpaired t-test, P >0.05 = statistically non-significant.

Table (21): ICU and hospital stays in the two studied groups.

Operative parameters	Regional PC		Remote PC		Significance	
	Mean	± SD	Mean	± SD	t	P
ICU stay (days)	2.01	0.87	1.85	0.88	0.348	0.257
Hospital stays (days)	7.78	1.46	6.58	1.55	0.312	0.229

t: unpaired t-test, P >0.05 = statistically non-significant, ICU: intensive care unit.

Gurung and Parajuli (2021) had similar echocardiographic parameters in both groups. They found that LVEF >55% in 20 cases (86.96%) and 20 cases (83.33%) in groups (1) & (2), respectively. LVEF 35-55% in 3 cases (13%) and 4 cases (16.7%) in groups (1) & (2), respectively. They all showed statistically insignificant difference (p >0.05). In agreement with other studies revascularization was done successfully with no new segmental wall motion abnormalities or contractility reduction. ECG was done in this study to show any cardiac arrhythmias or any postoperative ischemic changes.

Comparison between the two groups as regard postoperative ECG findings showed: ST-segment elevation in group(A) 6 cases while in group (B) were 9 cases. ST-depression in group (A) were 4 cases while in group (B) was one case only. LBBB: group (A) 4 cases, group (B) 3 cases. Abnormal Q-wave: group (A) 3 cases, group (B) 3 cases.
Non-significant difference (p >0.05) in all ECG parameters between both groups. In comparison between the pre and postoperative ECG in the regional PC showed ST-segment elevation preoperative 22 cases while postoperative were 6 cases: ST-depression preoperative 11 cases while postoperative were 4 cases. Abnormal Q-wave: preoperative 35 cases while postoperative were 3 cases. There was significant difference (p <0.05) in all ECG parameters. In comparison between the pre and postoperative ECG in the remote PC showed: ST-segment elevation preoperative 21 cases while postoperative were 9 cases. ST-depression preoperative 15 cases while postoperative was one case only. Abnormal Q-wave: preoperative 36cases while postoperative were 3 cases. There was significant difference (p <0.05) in all ECG parameters. All patients were managed postoperatively with vasodilators and antiplatelets and improved shortly.

Rahman et al (2010) had a similar study parameter An ECG was performed before surgery and on postoperative days 1 and 4. Perioperative myocardial infarction, assessed by an independent cardiologist, was defined by the presence of new left bundle-branch block or new Q waves of 2 mm in depth in 2 contiguous leads by postoperative day 4. Postoperative times in form of mechanical ventilation time, ICU time and hospital time. Mechanical ventilation time were in group (A) mean hours 20.64 except 16% of patients had been undergone prolonged ventilation for more than 24 hours, while group (B) mean hours 20.94 except 12% of cases had been undergone prolonged mechanical ventilation for more than 24 hours. Which were nonsignificant difference between both groups. ICU stay mean days were 2.01 in group (A) while in group (B) the mean days were 1.85. they showed insignificant difference between both groups (p >0.05). Hospital stay mean days were 7.78 in group (A) while in group (B) were 6.58. showed insignificant difference (p >0.05). In agreement with Rahman et al. (2010) the study applied on 90 patient who had undergone remote ischemic preconditioning versus controlled group (no ischemic preconditioning) and the average mechanical ventilation duration was ranged (14.9-15.5 hrs) in both groups, the length of ICU stay was 2-5 days in both groups and mean length of hospital stay was 8 days in both groups which were insignificant difference and similar to our study. Postoperative complications in ICU are related to other systems and comorbidities. It was observed that regional group had more complications than remote one. The most common complication was: low urine output in 7 cases in group (A) while group (B) were 8 cases, arrhythmias: there were 3 cases in group (A) undergone AF while group (B) were 2 cases and prolonged mechanical ventilation for more than 24 hours there was 8 cases in group (A) while group (B) were 6 cases. Clinical postoperative data in ICU of both groups include typical chest pain, positive inotropes or intra-aortic balloon pump insertion (IABP) only one case in group (A). They showed statistically non-significant difference (p >0.05). 30-day mortality we have 2 cases in group (A) and 1 case in group (B) which was non-significant.

Causes of mortality in group (A) which were 2 cases: case 1 due to deep sternal wound infection complicated with mediastinitis and septic shock. 2nd case was due to prolonged intubation with respiratory failure due to COPD. Group (B) mortality there were only one case due to fatal ventricular arrhythmias didn't respond to electrical or pharmacological cardioversion. Wang et al. (2019) stated that patients in the control group (regional PC) had a longer mechanical ventilation time than those in RIPC group (control vs. RIPC: 19.7 ± 2.9 h vs. 17.4 ± 3.8 h, $p < 0.05$), while had similar amount of time staying the Intensive Care Unit ($p > 0.05$) and in regular wards ($p > 0.05$). However, no significant differences were observed between the two groups during the period of observation. Remote ischemia preconditioning significantly shortens mechanical ventilation time and reduces myocardial damage by decreasing oxidative stress and reducing productions of inflammatory cytokines. RIPC reported to reduce the supportive ventilation time, confirming the beneficial effects of RIPC treatment in the process of CABG surgery and reduce ICU stay time and hospital stay (Azarfarin et al., 2014). In another study applied on patients had been undergone off-pump CABG using local preconditioning and another group without preconditioning, Laurikka et al. (2002) has noticed in hist study that two cycles of regional 2-min IP in the LAD, followed by 3 min of reperfusion, proved to be applicable and safe in patients undergoing off-pump myocardial revascularization, it tended to decrease the immediate myocardial enzyme release, it prohibited the postoperative increase in HR, and it enhanced the recovery of SVI.

According to Puskas et al. (2003) the study applied on 98 patients who had undergone off pump CABG without ischemic preconditioning and There were 3 deaths either in the hospital or within 30 days of surgery in the OPCAB group. All 3 patients in the OPCAB group who died were extubated on the day of surgery, had cardiac catheterization on postoperative day 1 demonstrating that all grafts were patent, and variously died later of fulminant pseudomembranous colitis on postoperative day 32, heparin-induced thrombocytopenia on postoperative day 44, and a primary arrhythmia on postoperative day 3. Renal failure 2%, atrial fibrillation 16% sternal wound infection 2% and new myocardial infarction was in 1% of the cases. According to Wu et al. (2018) study included 55 patients undergone RIPC and postoperative death was 1.82% of cases and acute kidney injury 16%. Also, Ahmad et al. (2014) study conducted to 35 patients undergone regional ischemic preconditioning and postoperative mortality was none while no conditioning group was 3, hemodynamic instability and IABP insertion was in 11.4% of preconditioning group.

7. Conclusions

According to our study in comparable with other studies, it showed a great outcome in myocardial contractility and low incidence of cardiac reperfusion injury for those being applied ischemic preconditioning. Regarding to remote and regional ischemic preconditioning, there were no significant difference in myocardial protection, reperfusion injury or postoperative outcome, however remote precondition is technically safer to be applied than regional coronary occlusion.

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