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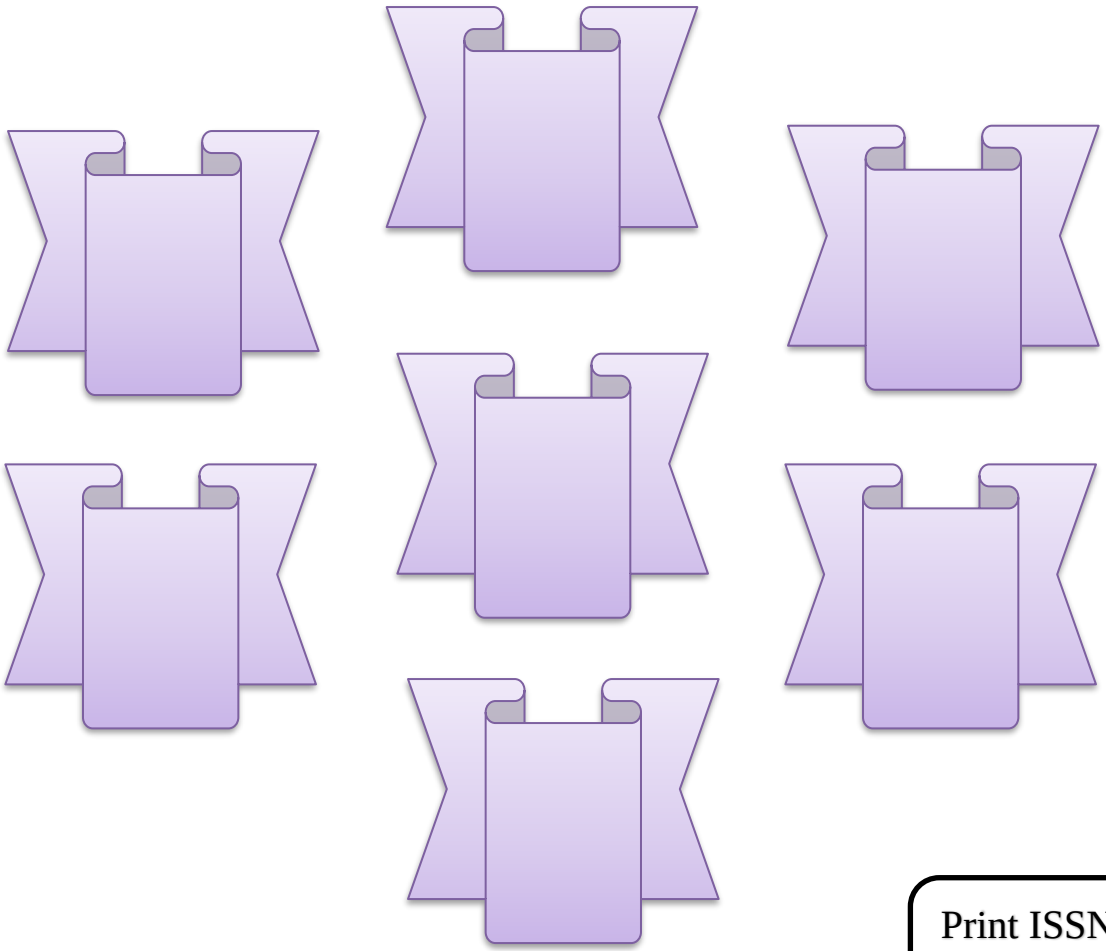

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Original Article

Effect of Remote Ischemic Preconditioning on Patient Survival and End Organ Injury During Elective Open Abdominal Aortic Surgery Repair: A Randomized Controlled Trial

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ABSTRACT

Background: Ischemic preconditioning is natural cyto-protective mechanism that can potentially protect end organs from ischemia. In examined instances having major vascular surgery, remote ischemia preconditioning provides straight-forward technique with the ability to set up widespread and systemic protection from significant organ harm. Thus, we have been required to assess clinical usage of remote preconditioning in preparing myocardial and renal protection after elective open Abdominal Aortic Aneurysm [AAA] repair in randomized trial.

Aim of the work: The aim of this research had been to examine potential of remote ischemic preconditioning on myocardial and renal protection and patient survival after elective open AAA repair.

Patients and Methods: This randomized double blinded clinical trial comparing AAA repair with remote ischemic preconditioning versus conventional AAA repair [control] was done in cardiothoracic and vascular surgery center Mansoura University from October 2022 to May 2023 after approval from institutional review board of Mansoura faculty of Medicine with obtaining a written informed consent from all studied cases.

Results: There had been statistically significant variation among studied groups as regard 30-day mortality.

Conclusion: Remote ischemic preconditioning improves mortality rate after elective open abdominal aortic surgery repair.

Keywords: Ischemia; Preconditioning; End organ injury; Aorta; Abdominal surgery repair.

INTRODUCTION

Myocardial and renal injuries commonly contribute to perioperative morbidity and mortality after abdominal aortic surgery. Brief durations of ischemia followed by reperfusion in an organ have been known to give systemic protection from long ischemia, phenomenon known as remote ischemic preconditioning [1].

After elective abdominal aortic surgery, the most common reason for both early and late mortality has been cardiac-related [1]. Mechanism of myocardial injury remain unclear and evidence exists that most cardiovascular events in vascular surgery cases have been consequence of non-hemodynamically significant stenosis [2].

Irrespective of the mechanism, studied cases undergoing abdominal aortic surgery remain at high risk for cardiovascular events [3]. Subclinical myocardial injury after major vascular surgery, discovered by increase in cardiac troponin, has been common and has been related to increased mortality [4, 5].

Ischemic preconditioning is a phenomenon that occurs when small period of ischemia has been followed by reperfusion before prolonged ischemic episode, potentially preparing the body to resist cellular damage. Several signal trans-duction pathways have been activated by the initial ischemia event, maintaining myocyte contractility and function [6].

Lately, it is illustrated that ischemia at location distal to heart can confer same cellular protection in circulating or neuroprotective mediators released from distant organs subject to ischemia [7]. Other organs at risk of ischemia throughout surgery may benefit systemically from this kind of remote preconditioning [1, 8].

Renal injury, result of hemodynamic variations after application of aortic cross-clamp and ischemia–reperfusion injury after its release, has been common reason for morbidity and mortality after elective abdominal aortic surgery [1, 8]. Acute renal failure occurs in approximately ten percent of studied cases after elective open abdominal aortic aneurysm [AAA] repair [9] and has been independent predictor of death [1].

In examined instances having major vascular surgery, remote ischemia preconditioning provides straightforward technique with the ability to set up widespread and systemic protection from significant organ harm. Thus, we have been required to assess clinical usage of remote preconditioning in preparing myocardial and renal protection after elective open AAA repair in randomized trial.

To examine whether remote preconditioning decreases incidence of myocardial, renal injury and survival rate in studied cases undergoing elective open abdominal aortic surgery, we did randomized trial.

THE AIM OF THE WORK

In this study, we compared AAA repair with remote ischemic preconditioning versus conventional AAA repair [control]. Primary outcome measure had been myocardial injury and rise in serum cardiac troponin I. Secondary outcome involved myocardial infarction, renal impairment and death due to bleeding, cardiac cause, infection intestinal ischemia or multiple organ failure.

PATIENTS AND METHODS

This randomized double-blinded clinical trial comparing AAA repair with remote ischemic preconditioning versus conventional AAA repair [control] was done in Cardiothoracic and vascular surgery centre, Mansoura University from October 2022 to May 2023 after approval from institutional review board of Mansoura faculty of Medicine at 22 May 2023 with a reference number [R.23.05.2157] with obtaining a written informed consent from all studied cases.

Studied cases assigned for primary elective open AAA repair had been asked to take part in research at period of scheduling for operation.

Exclusion criteria: Potential individuals was excluded if they > 90 years old, require concomitant processes other than AAA repair, had experienced acute coronary syndrome or myocardial infraction in 3 months, are incapable of giving informed consent, or taking sulfonylureas oral hypoglycemic agents or nicorandil drug therapy as these agents are revealed to affect preconditioning [10, 11].

Randomization: Computer-generated list of studied cases had been used to randomly assign them to blocks that had been then covered up with numbered, sealed, opaque envelopes. Allocation had been announced by operating

surgeon by opening top envelope on morning of operation. Studied cases were blinded to technique and results. Also, data collectors were blinded to technique and results. Assignment of cases and findings was compared and analyzed blind in two groups labeled R and C. **Group R:** group of AAA repair with remote ischemic preconditioning. **Group C:** conventional AAA repair [control group].

Procedure

All studied cases were evaluated pre-operatively by history taking, clinical testing, basal laboratory investigations [complete blood picture, INR, liver function and kidney function tests], ECG and ECHO. To evaluate valve function, contractility, or existence of aberrant regional wall motion, transthoracic echocardio-graphy was performed on every studied case. cardiologist evaluated studied cases who had cardiac symptoms and then referred them for non-invasive stress testing, while required by the clinical guidelines. Cases had been referred for coronary angiography if the previous evaluation became unfavourable or if their symptoms changed. Subsequently, revascularized studied cases became eligible for inclusion. In lack of preoperative contraindications, β-blockers had been administered.

For all studied cases under local anesthesia, radial arterial cannula and central venous line were inserted. Prior to inducing anesthesia, an epidural catheter had been placed into the L3-L4 intervertebral region to cover the region of lower abdomen.

After preoxygenation with one hundred percent oxygen, anesthesia had been induced in patients with good cardiac function [no chest pain, no dyspnoea, normal heart rate and no syncope] gently with intravenous fentanyl [1–2 μg/kg], propofol [1-2 mg/kg] and atracurium [0.5 mg/kg]. In cases with poor cardiac functions induction was done by opioid based anesthesia; intravenous fentanyl [2–4 μg/kg], midazolam [1-2 mg] and atracurium [0.5 mg/kg]. After tracheal intubation and start of mechanical ventilation, anesthesia had been preserved with isoflurane [1–1.5%] or sevoflurane [1.5-2%] according to cardiac function, atracurium [0.5 mg/kg/h] and oxygen: air [50: 50%]. Intraoperative monitoring of oxygen saturation, heart rate, ECG, invasive blood pressure, central venous pressure, capnography was done.

In the remote ischemic preconditioning [RIPC] group, sequential ischemia of upper limbs was induced through applying of non-invasive pressure cuff on the right arm two fingers above cubital fossa and elevating its pressure above the patient systolic pressure by 40 mm hg with ten minutes ischemia time followed by ten minutes reperfusion during which same ischemia is induced in the left arm for 10 minutes then reperfusion for 10 minutes. Ischemia reperfusion was repeated sequentially in both arms with a total ischemia time 20 minutes in each arm with 10 minutes reperfusion in between. Sequential ischemia in both arms will minimize repeated ischemia in a single arm, therefore decreasing potential for trash arm.

Surgical dissection had been completed up until moment surgeon had been getting ready to cross-clamp aorta and access aneurysm sac. At this time, all patients were heparinized.

Serum lactate and ABG were measured after RIPC, and after declamping. Bolus dosages of fentanyl, raising isoflurane concentration, or adding nitroglycerin infusion were used to treat hypertension while clamping. Fluids, bolus ephedrine doses, decreasing isoflurane concentration, and, if necessary, norepinephrine infusion after declamping were used to treat hypotension. Atropine [30 g/kg] had been administered in bolus dosages to treat bradycardia. Cases with surgery above the origin of the renal artery received crystalloids [500–1000 ml], mannitol twenty percent [one hundred ml] and furosemide [forty mg] through thirty min before clamping for renal protection. At end of the procedure and after emergence from anesthesia, cases had been transferred to Intensive Care Unit with close monitoring.

Following surgery, all studied cases received bupivacaine and fentanyl epidural analgesia & studied case-controlled intravenous morphine. In lack of any contraindications, studied cases who had myocardial damage or infarction were then treated routinely with antiplatelet medications [Aspocid] immediately after surgery, beta-blockers and angiotensin-converting enzyme inhibitors.

Collected data: Basal serum creatinine, cardiac troponin, ABG, serum lactate. ABG and serum lactate before and after declamping. **The primary result measure** had been myocardial damage described as rise in blood cardiac troponin more than 0.40 ng/ml.

Secondary results involved mortality, kidney damage and myocardial infarction. revised American College of Cardiology/ American Heart Association recommendations described myocardial infarction as TnI spike >1.5 ng/mL with at least 1 of following: typical ischemic symptoms, ECG alterations indicative of ischemia, or new pathological Q-waves. Each morning following surgery, 12-lead ECG were done as required by clinical guidelines. In accordance with recommendations studied cases undergoing major vascular surgery and noncardiac surgery, impaired renal function has been characterized as peak serum creatinine level of > 177 μmol/L [2.0 mg/dL] [5]. Blood specimens was taken preoperatively and on morning of postoperative days; first, third, and seventh day post-operatively.

Statistical analysis: When appropriate, data had been statistically definite using the mean ± standard deviation, or frequencies [number of occurrences]. Student's t test for independent samples had been used to compare numerical variables among study groups. The paired t test had been used to compare numerical variables within groups. Using the Chi square test, categorical data were compared. When expected frequency has been < five, Fisher's exact test had been used instead. P <0.05 had been regarded as statistically significant. SPSS [Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA] version 15 for Microsoft Windows had been used to do all statistical calculations. Data had been input into computer and analyzed using IBM SPSS software package version 20.0. IBM Corp., Armonk, New York Number and percentage had been used to define qualitative data. normality of distribution had been examined using Kolmogorov-Smirnov test. range [minimum and maximum], mean, standard deviation, median and interquartile range had been used to indicate quantitative data. At five percent level, significance of findings had been decided. used tests had been Chi-square test: for comparing numerous groups for categorical variables Student t-test: To compare 2 groups under study for quantitative variables with normally distributed distributions.

RESULTS

Table [1] displays that there had been no statistically significant variation among studied groups as regard baseline data.

Table [2] shows that there had been statistically significant difference among studied groups as regard operative data.

Table [3] shows that there had been statistically significant difference among studied groups as regard 30-day mortality.

Table [1]: Baseline characteristic of the studied cases

		Group R [n = 38]		Group C [n = 38]		Test	P
Age [years]	Range Mean ± SD	59 – 83 72.71 ± 7.27		60 – 84 73.45 ± 7.25		t= 0.442	0.660
Gender, n [%]	Females Males	4 [10.5%] 34 [89.5%]		5 [13.2%] 33 [86.8%]		χ^2= 0.126	0.723
BMI	Range Mean ± SD	24.7 – 29.1 26.9 ± 1.35		24.7 – 29.1 26.84 ± 1.27		t= 0.193	0.848
Smoking, n [%]		19 [50%]		20 [52.6%]		0.053	0.818
Previous medical record							
Ischemic heart disease		7	18.4	8	21.1	0.083	0.773
Myocardial infarction		6	15.8	9	23.7	0.748	0.387
CABG/PCI		8	21.1	10	26.3	0.291	0.589
Stroke/TCI		2	5.3	5	13.2	1.416	0.234
Vascular surgery		3	7.9	2	5.3	0.214	0.644
Diabetes		3	7.9	4	10.5	0.157	0.689
Atrial fibrillation		9	23.7	6	15.8	0.748	0.387
COLD		6	15.8	3	7.9	1.134	0.287
Cancer		3	7.9	3	7.9	0.0	1.0
Hypertension		20	52.6	27	71.1	2.732	0.098
Preoperative medication							
Antiplatelet		13	34.2	11	28.9	0.244	0.622
Anticoagulant		1	2.6	3	7.9	1.056	0.304
Lipid-lowering		18	47.4	13	34.2	1.362	0.243

Table [2]: Comparing among cases according to operative data

		Group R [n = 38]	Group C [n = 38]	Test	p
Duration of operation [min.]	Range Mean ± SD	67 – 288 171.74 ± 71.55	76 – 289 177.18 ± 66.53	t= 0.344	0.732
Red blood cell transfusion [units]	Range Mean ± SD	0 – 18 8.32 ± 5.57	0 – 20 9.66 ± 6.78	t= 0.943	0.349
Plasma [units]	Range Mean ± SD	1 – 11 5.53 ± 3.01	0 – 13 6.42 ± 4.49	t= 1.020	0.311
Platelets [units]	Range Mean ± SD	0 – 4 1.76 ± 1.48	0 – 5 2.29 ± 1.58	t= 1.502	0.137
Bifurcated prosthesis, n [%]		20 [52.6%]	18 [47.4%]	χ^2= 0.211	0.646

SD: Standard deviation; χ^2: Chi square test; t: student t-test

Table [3]: Comparing among cases according to outcome

	Group R [n = 38]		Group C [n = 38]		Test	P
	No.	%	No.	%	χ^2	P
Myocardial infarction	17	44.7	12	31.6	1.394	0.238
30-day mortality	7	18.4	15	39.5	4.094	0.043*
Cause of death						
Bleeding	2	5.3	1	2.6	6.652	0.466
Cardiac	1	2.6	2	5.3		
Infection	0	0	1	2.6		
Intestinal ischemia	1	2.6	4	10.5		
Multiple organ failure	2	5.3	4	10.5		
Pulmonary	1	2.6	2	5.3		
Renal	0	0	1	2.6		
Multiple organ failure	5	13.2	7	18.4	0.396	0.529
Intestinal ischemia	3	7.9	6	15.8	1.134	0.287
Dialysis	8	21.1	6	15.8	0.350	0.554
Stroke	1	2.6	1	2.6	0	1.0

χ^2: Chi square test

DISCUSSION

Using a technique called remote ischemic preconditioning, short, intermittent bursts of ischemia & reperfusion [IR] shield distant organs from longer bursts of IR harm. RIPC is carried out with numerous cycles of IR employing blood pressure cuff on studied case's limb in studied cases undergoing heart surgery [12].

We had been interested in learning which population would profit most from numerous randomized control studies that are done, results of which are diverse. We investigated whether it's necessary to modify RIPC technique for various studied case populations and whether advancements in surrogate markers result in better clinical results. We feel that area under curve decrease in cardiac biomarkers gives superior evidence of cardio-protection than time-point measurements, which are often used in majority of meta-analyses that have been published up to this point to report on cardiac protection, like at twelve h postintervention [13].

In this study, we showed that there had been no variation among studied groups as regards baseline data. In a study to assess RIPC versus no preconditioning in prevention of perioperative myocardial infarction throughout open surgery throughout for ruptured abdominal aortic aneurysm, **Pedersen *et al.*** [14] found that baseline characteristics had been alike among 2 groups. **Murphy *et al.*** [15] discovered that among 62 studied cases presenting for open AAA repair involved in this research; thirty-one studied cases had been randomized to RIPC group and thirty-one studied cases had been randomized to control group [conventional open AAA repair], there had been no statistically significant variation among studied groups as regard baseline data.

In this study we illustrated that there had been no variation among studied groups as regard operative data. **Pedersen *et al.*** [14] discovered that utilization of platelets & plasma, as well as time of process, did not significantly change among 2 groups. type of graft [tube/bifurcated] used had been same. **Murphy *et al.*** [15] found that Aortic cross-clamp duration, application site, or graft type did not differ significantly from one another. **Meybohm *et al.*** [16] found that control and RIPC groups' demographic & surgical data did not significantly change from one another.

In this investigation, we discovered statistically significant variation in thirty-day mortality among analyzed groups. Current detailed meta-analysis by **Ali *et al.*** [17] revealed indications of decreased mortality related to ischemic cardiac events & decrease in combined endpoint of significant adverse cardiovascular events, but also shown that incidence of periprocedural myocardial infarction had been decreased by RIPC while had been post-procedural peak release of troponin. **Pedersen *et al.*** [14] found that mortality risk decreases of fifteen percent in absolute terms at thirty days, resulting in OR of 0.46 [95% CI 0.22 to 0.99].

Zarbock *et al.* [18] observed that RIPC significantly shortened length of stay in intensive care unit [three days [interquartile range, two-five] vs. four days [interquartile range, two-seven] [P =.04] & had no impact on myocardial infarction, stroke, or mortality. **Choi *et al.*** [19] showed that mortality rate was lower in remote ischemic preconditioning group than in control group. **Hong *et al.*** [20] found that following surgery, RIPC group experienced in-hospital mortality at rate of 1.6 percent compared to control group's 2.2 percent [P = 0.3]. **Luo *et al.*** [21] found that there was fewer mortality in remote ischemic preconditioning group in forty-eight h after surgery compared with control group [1.5% vs. 4.5%; P=0.004; relative risk, 0.43; 95% confidence interval, 0.24–0.76; absolute risk reduction, 0.27; 95% CI, 0.10–0.42].

More recently, **Cheung *et al.*** [22] reported 1st human clinical use of remote conditioning. In this randomized, controlled trial, authors used blood pressure cuff to administer forty five-minute cycles of lower limb ischemia/ reperfusion to children undergoing heart surgery to induce remote preconditioning. In their investigation, remote preconditioning decreased airway resistance, postoperative inotropic needs, and myocardial damage. These data from randomized, controlled trials support conclusion from our research that remote preconditioning has been reasonable therapeutic approach to lessen ischemia harm in human sensitive organs.

Hu *et al.* [23] Researchers who investigated use of RIPC for CI-AKI prophylaxis hypothesized that RIPC had been linked to reductions in-hospital mortality & duration of stay. **Pei *et al.*** [24] perioperative incidence of CI-AKI in studied cases receiving elective coronary intervention was considerably decreased by RIPC [P = 0.04].

In summary, our research demonstrates that remote ischemia preconditioning reduces mortality after elective open abdominal aortic surgery.

Conflict of Interest and Financial Disclosure: None.

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