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The cardioprotective effect of intralipid in decreasing the ischemic insults during off-pump coronary artery revascularization

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Abstract

Background: Off pump coronary artery revascularization (OPCAB) surgeries have benefits over the conventional on pump cardiac surgery, because it avoids the trauma caused by cardiopulmonary bypass (CPB) and minimize aortic manipulation. However, some disadvantages of OPCAB include the concern of ineffective coronary revascularization. Some drugs have shown the ability to protect the myocardium in different studies, by different methods. The usage of intralipid has been shown to make a better functional recovery of the cardiac muscles and help to decrease the myocardial infarct size, it shortens the action potential time, which show polyunsaturated fatty acids diets mechanism as an antiarrhythmic drug, and are associated with low incidence of coronary artery disease.

Methods: We divided patients into two groups according to the randomization envelopes: intralipid group (group A) received 1.5 ml/kg intralipid 20% through central venous line after sternotomy over 1 h and during infusion, blood pressure, heart rate, and temperature were monitored all through the infusion time. Control group (group B) received normal saline 0.9% in the same volume over the same duration.

Results: This study showed that infusion of 1.5 ml/kg intralipid after sternotomy in off pump coronary artery revascularization given as preconditioning agent improve the myocardial ischemia reperfusion injury, decrease the need for high doses of nor adrenaline infusion after revascularization, earlier normalization in troponin levels starting 24 h after surgery and higher values of cardiac index were measured in ICU using PICCO.

Conclusions: This study showed the benefits of infusion of 1.5 ml/kg of intralipid after sternotomy, in preconditioning during OPCABG. Preconditioning with intralipid proved to decrease reperfusion injury in myocardium expressed by improvement in cardiac functions (EF and cardiac index) and normalization of specific cardiac marker (cardiac troponin I).

Keywords: OPCAB, Myocardial ischemia, Preconditioning, Intralipid, Myocardial protection

Background

First operated coronary revascularization procedures were done in the early 1960, operated on the beating heart without cardiopulmonary bypass (CPB). Afterwards, the technique was stopped due to the developments of CBP machine that was able to improve myocardial preservation techniques that made it a safer surgery. Despite improvement in protection strategies, ischemia still results in ischemic reperfusion injury during coronary artery bypasses grafting (CABG). Off-pump coronary surgery (OPCAB) does not eliminate the risks of ischemia-reperfusion injury (Puskas et al. 2016).The advantages of OPCAB were based on their benefits over the limitations of traditional on-pump coronary artery bypass surgery, because it avoids the trauma caused by cardiopulmonary bypass (CPB) and minimize aortic manipulation, so decreases the mortality,

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perioperative neurological events, transfusions of blood product, renal failure, and hospital stay. OPCAB disadvantages include the concerns about incomplete quality of revascularization that could increase the need for redo revascularization and cause late mortality (Ohmes et al. 2017). As regards patients treated with thrombolytic therapy, this technique is not effective so a pharmacologic post-conditioning is still in need. The ideal agents must be safe and effective in improving the ischemia/reperfusion injury (Li et al. 2017). Some drugs have been shown in different studies to protect the myocardium, for example, cardio-selective β1-blocker and adenosine triphosphate-sensitive potassium channel openers (Siamak et al. 2011). Now intralipids have received attention in cardiovascular studies as polyunsaturated fatty acid-rich diets are associated with low incidence of cardiac damage. Administration of polyunsaturated fatty acids to cardiac myocytes shorten the action potential time, and act as an antiarrhythmic drug, and are associated with low incidence of coronary artery disease. Recently, post-ischemic treatment with intralipid has shown to enchance the cardiac functional recovery of isolated mouse hearts by ~ 4 fold and reduce myocardial infarct size by 70%. Intralipid 20% is an emulsion of soybean oil (20%), egg yolk phospholipids (1.2%), and glycerol (2.2%) (Rahman et al. 2011a).

Methods

We divided patients into two groups according to the randomization envelopes: intralipid group (group A) received 1.5 ml/kg intralipid 20% through central venous line after sternotomy over 1 h and during infusion, blood pressure, heart rate, and temperature were monitored all through the infusion time. Control group (group B) received normal saline 0.9% in the same volume over the same duration.

Aim of the work

The aim of the study was to assess the effect of intralipid regarding efficiency in lowering myocardial ischemia in off pump coronary artery revascularization surgery and to evaluate the reduction of postoperative ventilation duration and the length of hospital stay.

Study design

This study was a prospective, randomized, double-blinded, placebo-controlled trial. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Randomization was performed using sequentially numbered closed envelopes.

The study was conducted on (48) patients scheduled for off-pump coronary artery bypass graft surgery.

Inclusion criteria

Age between 40 and 75 years old with history of multiple vessel disease who was candidate for coronary revascularization by off pump technique.

Exclusion criteria

The patients with the following criteria were excluded: (a) age less than 40 or more than 75 years; (b) ejection fraction less than 50%; (c) those who had an emergency surgery or patients scheduled for valve surgery with coronary revascularization or redo procedures; and (d) those who had a history of allergy to peanuts, eggs, and soya beans (these are intralipid ingredients).

After the consent and explanation about the steps of research, anesthesia team discussed with cardiac surgeons the expected potential benefits from intralipid infusion and took their approval; then, the subjects of both groups were subjected to the following clinical parameters: complete history taking, clinical examination, and laboratory profile: CBC, liver function tests (including coagulation profile, liver enzymes, albumin, bilirubin), viral markers: (HCVAb-HBsAg), INR, serum creatinine, serum urea, Na^+ and K^+ level, serum troponin, CK total, CK MB, and complete lipid profile. Radiological assessment including the following: chest X-ray, ECG, echocardiography, and carotid duplex for patients above 60 years old.

Patients were divided into two groups according to the randomization envelopes: the intralipid group (group A) received 1.5 ml/kg intralipid 20% (INTRALIPID by Fresenius Kabi) through central venous line after sternotomy over 1 h and during infusion, the blood pressure, heart rate, and temperature were closely monitored during the infusion time. The control group (group B) received normal saline 0.9% 1.5 ml/kg over same duration. At the operation theater, the team was blinded to the group assignments by covering the drugs infusion pumps and lines for blinding purpose of the study.

Standard intraoperative monitoring consisted of pulse oximetry and 5 lead ECG was applied on all patients, then cannulation of left radial artery was done by local anesthesia, followed by central venous catheter insertion in right internal jugular vein after local anesthesia by ultrasound-guided technique. Radial cannula and central line insertion were performed by the senior anesthetist. Urinary catheter was inserted after endotracheal intubation for monitoring urine output.

Anesthesia was induced with fentanyl 5–10 μg/kg, midazolam 0.1–0.5 mg/kg, and cis-atracurium 0.15 mg/kg. Then, anesthesia was maintained with isoflurane1–1.5% and continuous infusion of fentanyl at 0.2 μg/kg/h and cis-atracurium infusion 2 μg/kg/min. Then, nasopharyngeal temperature probe was inserted immediately after endotracheal intubation. Transesophageal Echo (TEE) was used to assess the ventricular function. The infusion of the studied drugs was started after sternotomy through the internal jugular vein, after left internal mammary artery harvesting 100 IU/kg heparin was given to achieve ACT level 280–300 s. Then, after the proximal anastomosis, the neutralization of heparin action was done by injecting protamine, at ratio of 1 mg protamine for 100 IU heparin. Inotropic support started by titration of Norepinephrine 0.01–0.3 μg/kg/min, started with revascularization and continued according to the patients' hemodynamics in the first 12 h after surgery.

Patients were extubated in the ICU after confirming hemodynamically stable data with normal blood gases. The time of extubating the patients and the length of stay in ICU for all patients was recorded. Fat given in the intralipid group was cleared after 5–6 h, depending on normal renal clearance (patients included in the study had normal kidney profile). No follow-up lipid profile was done postoperatively (Ayres et al. 2014). Blood samples were collected starting from after sternotomy time, then every 6 h for the first 48 h after CPB, for the measurement of cardiac troponin (CTnI) and cardiac-specific creatine kinase (CK-MB). The blood samples were sent to the laboratory for analyzing CTnI and CK-MB using commercial enzyme-linked immunosorbent assay kits (Beckman, Fullerton, CA, USA). Continuous systemic arterial blood pressure was done by invasive radial artery monitoring for all patients. TEE was used to assess ventricular functions and systemic vascular resistance intraoperatively and postoperatively till extubating the patient then PICCO for assessing cardiac output and measure systemic vascular resistance.

Statistical analysis

The statistical analysis was performed using a standard SPSS software package version 23 (Chicago, IL). Data were tested for normality using the Kolmogorov–Smirnov test. Normally distributed numerical data are presented as mean ± SD and differences between groups were compared using the independent Student's t test, data not normally distributed were compared using Mann-Whitney test and are presented as median(IQR) and categorical variables were analyzed using the χ^2 test or Fisher exact test and are presented as number. All P values are two-sided. $P < 0.05$ is considered statistically significant.

Table 1 Demographic data

	IL group (*n* = 23)	NS group (*n* = 23)	*P* value
Age (years)	55.74 ± 7.7	55.6 ± 6.6	**0.87**
Sex (M/F)	12/11	14/9	**0.76**
DM	14	12	**0.767**
HTN	11	14	**0.554**
Previous cardiac events			
- No events	10	6	**0.464**
- NSTEMI	7	9	
- Stable angina	6	8	

Data are presented as mean ± SD, number of patients and ratio $p > 0.05$ is considered statistically non-significant

DM Diabetes mellitus, *HTN* Hypertension, *NSTEMI* Non-ST segment elevation myocardial infarction

Results

This study was conducted on 48 patients; 2 patients were removed from the study due to change in the surgical decision and on pump CABG was performed, leaving 23 patients in each group. Patients baseline data and preoperative hemodynamics were recorded and no difference between 2 groups were recorded (Table 1). Patients intraoperative data (systolic and diastolic blood pressure after induction and after reperfusion) (Fig. 1), heart rate, and central venous pressure (CVP) were recorded and no difference between 2 groups, except diastolic blood pressure showed significant difference in the intralipid group after revascularization P value < 0.001 (Table 2). After revascularization, both groups were compared as regards the need for vasopressor or inotropes and the doses used after the reperfusion. The results showed statistically significant difference in intralipid group detected by the decrease of the dose of nor adrenaline used P value 0.019 (Table 3). With respect to the cardiac biomarkers represented in troponin level measurement which was started after sternotomy and then every 6 h up to 48 h in the ICU (Fig. 2), data analysis showed improvement in the intralipid group by the decrease in the level of troponin started after 24 h postoperative in ICU P value 0.007 (Table 4). In this study, by comparing both groups as regards the

Table 2 Intraoperative hemodynamics

	IL group (*n* = 23)	NS group (*n* = 23)	*P* value
SBP (induction) mmHg	137.8 ± 23.15	140.8 ± 20.64	**0.64**
DBP (induction) mmHg	82.2 ± 13.13	86.5 ± 9.8	**0.21**
SBP (after CPB) mmHg	107.1 ± 6.42	96.74 ± 26.7	**0.149**
DBP (after CPB) mmHg	72.8 ± 14.1	56.74 ± 11.8	**< 0.001***
Heart rate (b/m)	88.1 ± 11.54	91.3 ± 11.68	**0.357**

Data are presented as mean ± SD

SBP Systolic blood pressure, *DBP* Diastolic blood pressure, *HR* Heart rate, *HR* Heart rate, *mmHg* millimeter mercury, *B/m* beat/minute

* P value < 0.001 is considered statistically significant

Table 3 Doses of inotropes used

	IL group (*n* = 23)	NS group (*n* = 23)	*P*-value
Nor adrenaline (μg/kg/min)	0.05 (0.03–0,1)	0.12 (0.05–0.2)	**0.019***
Adrenaline (μg/kg/min)	0 (0–0.3)	0.03 (0–0.05)	**0.065**
ST segment elevation (/pt)	2	6	**0.243**

Data are presented as median (IQR) or number of patients
μg/kg/min microgram/kilogram/minute, *pt* patient
**P* value <0.05 is considered statistically significant

cardiac function represented by ejection fraction by trans-esophageal ECHO intraoperative before and after reperfusion, it showed no statistically significant difference, but when comparison was done postoperatively in ICU using PICCO for measurement of cardiac index, it showed statistically significant difference represented by *P* value 0.001 (Table 5).

Discussion

The reperfusion injury is still one of the major factors that affect patients' cardiac function after surgery. Ischemic preconditioning and/or post-conditioning has been shown to be able to decrease the reperfusion injury. Although multiple drugs were tested, no drug was proved to be effective in large-scale studies for protection of the myocardium. Intralipid may have a potential role in cardio protection (Kawaraguchi et al. 2011). Murry and coworkers (1986) discovered that the heart could be 'conditioned' to protect itself against myocardial infarction (Murry et al. 1986). Study in 1993 demonstrated that ischemic preconditioning (IPC) could be caused in patients undergoing CABG by clamping the aorta for 2 min and unclamping for another 2 min to induce short episodes of myocardial ischemia and reperfusion before inducing the sustained global myocardial ischemia induced by cross-clamping of the aorta. They found that patients that received IPC at the time of surgery had preserved ATP levels in ventricular biopsies and decreased myocardial injury (Oosterga et al. 2001). Several studies have investigated IPC in CABG surgery, the results were summarized in a published meta-analysis of 22 studies (933 patients). The studies concluded that IPC was associated with less ventricular arrhythmias, fewer inotropic requirements, and decrease ICU stay (Walsh et al. 2008). As proved before, preconditioning technique have adequate myocardial protection during CABG surgery; however, the disadvantages of the usage of ischemic preconditioning techniques (risk of arterial thrombo-embolism resulting from cross-clamping and declamping the aorta was avoided by using pharmacological drug in preconditioning and improve myocardial protection) (Pierce et al. 2017). Lipids as polyunsaturated fatty acid-rich diets have received research attention. Lipids proved to be able to decrease cardiac insults. Intralipid has been shown to be cardioprotective (Li et al. 2012). The mechanism(s) of cardiac protection by intralipid was investigated, especially the role of glycogen synthase kinase3β (GSK-3β) and mitochondrial permeability transition pore. In vivo rat hearts or isolated mouse hearts were subjected to ischemic insult then, reperfusion was done using Intralipid (1% in ex vivo and one bolus of 20% in in vivo). The hemodynamic function, infarct size, threshold for the opening of mitochondrial permeability transition pore (mPTP), and phosphorylation levels of protein kinase B (Akt)/ extracellular signal regulating kinase (ERK)/GSK-3β were measured. Reperfusion by intralipid developed 70% reduction in infarct size in the in vivo rat model (Rahman et al. 2011b). The (mPTP) in myocardial muscle is a non-selective conductance pore found in the inner mitochondria membrane. The mPTP is closed during ischemia, but opens during the reperfusion time. Opening of the mPTP is affected by ischemia and reperfusion, formation of reactive oxygen radicals, and accumulation of Ca^{2+}in the mitochondrial matrix. Delaying the opening of the mPTP after reperfusion has been a target to lower the development of myocardial injury. Intralipid demonstrated stops the opening of the mPTP and protects the heart by recruiting the reperfusion injury salvage kinase pathway (Griffiths and Halestrap 1991). Our finding went with the study performed by Yuan Y. and coworkers in July 2019 testing the outcome of intralipid post-conditioning in adult. They enrolled 1000 participants undergoing CPB for any elective adult cardiac surgical procedures. They concluded a rationale for

Table 4 Troponin level measurement every 6 h

	IL group (*n* = 23)	NS group (*n* = 23)	*P* value
Set 1 (ng/ml)	0.04 (0.01–0.08)	0.04 (0.03–0.05)	**0.37**
Set 2 (ng/ml)	0.1 (0.06–0.5)	0.09 (0.08–0.4)	**0.689**
Set 3 (ng/ml)	0.3 (0.1–0.6)	0.2 (0.1–0.5)	**0.991**
Set 4 (ng/ml)	0.4 (0.2–0.5)	0.5 (0.3–0.8)	**0.08**
Set 5 (ng/ml)	0.3 (0.1–0.5)	0.8 (0.425–1.6)	**0.007***
Set 6 (ng/ml)	0.2 (0.1–0.5)	0.8 (0.4–1.8)	**0.002***
Set 7 (ng/ml)	0.1 (0.08–0.4)	0.5 (0.2–1.8)	**0.004***
Set 8 (ng/ml)	0.008 (0.05–0.2)	0.25 (0.1–1.65)	**0.008***
Set 9 (ng/ml)	0.06 (0.05–0.1)	0.07 (0.05–1.2)	**0.21**

Data are presented as median (IQR)
ng/ml nanogram/milliliter
**P* value <0.001 is considered statistically significant

Table 5 Ejection farction and cardiac index

	IL group (n = 23)	NS group (n = 23)	P value
E F after induction (%)	0.57 (0.5–0.61)	0.54 (0.46–0.59)	**0.276**
EF after revascularization (%)	0.6 (0.55–0.65)	0.59 (0.47–0.64)	**0.28**
Cardiac index by (PICCO) (L/min/m^2)	3.08 ± 0.62	2.35 ± 0.42	**< 0.001***

Data are presented as median (IQR), mean ± SD. *P* value < 0.001 is considered statistically significant
EF Ejection fraction, *PICCO* Pulsed-induced contour cardiac output
L/min/m^2 liter/minute/m^2

evaluation of relevant benefit of intralipid therapy (Yuan et al. 2020). In this study, post-ischemia and reperfusion injury in myocardium detected by the specific cardiac markers (cardiac troponin I) and detected by changes in cardiac function following reperfusion represented as EF and cardiac index showed decrease in cardiac biomarkers in intralipid group and improvement of cardiac index. In this work, it was noticed that the hemodynamic differences, the usage of vasopressor and/or inotropes,

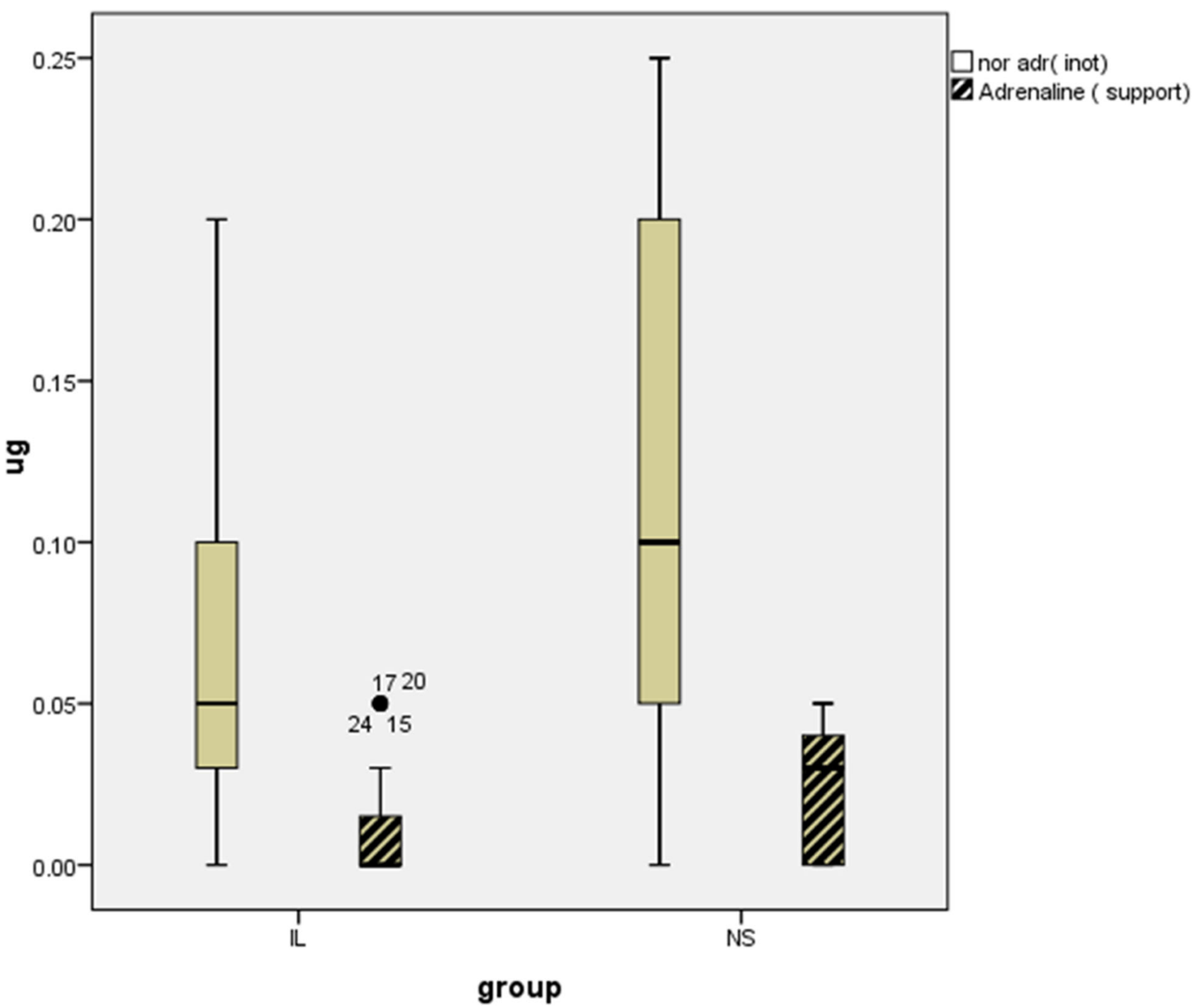
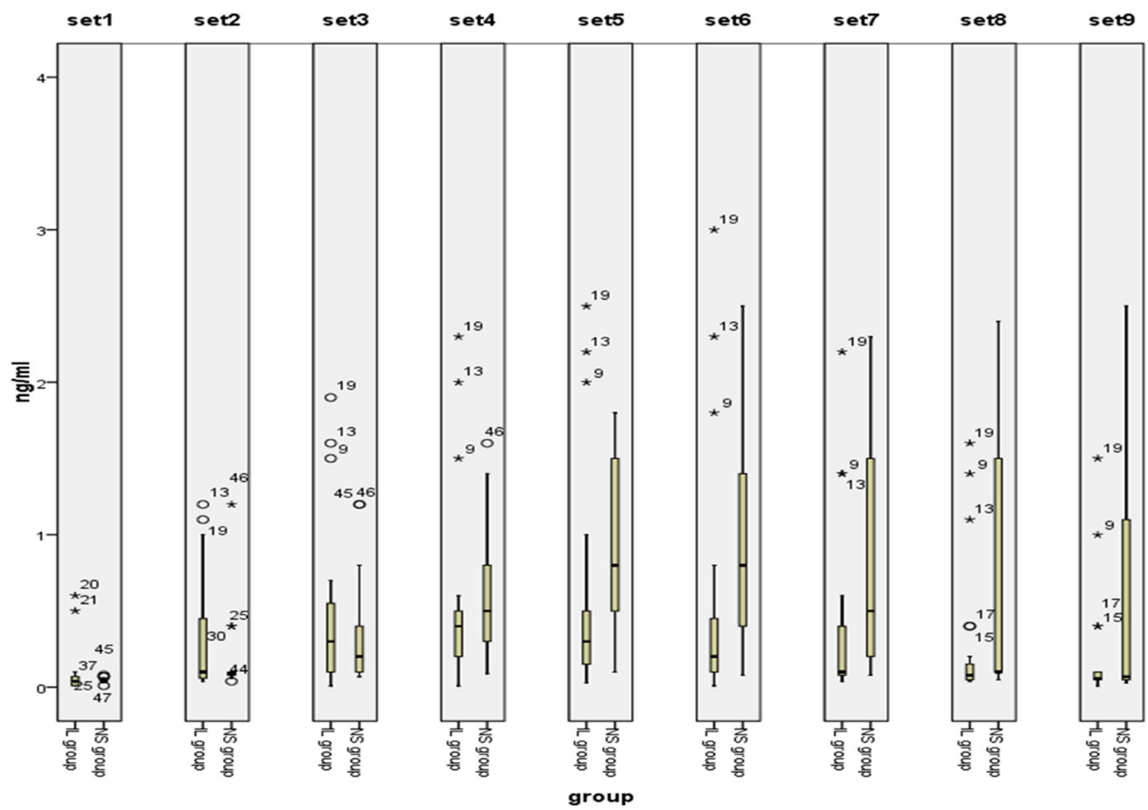


Fig. 1 Types and doses of inotropes. The middle black solid line represents the median, the upper and lower margins of each box are the IQR, whiskers are maximum and minimum values, and dot represent the number of patient with outlier data. Data are presented as mean ± SD. *P value < 0.001 is considered statistically significant



Data are presented as mean± SD

*p-value < 0.001 is considered statistically significant

Fig. 2 Different sets of tropnin I taken every 6 h. The middle black solid line represents the median, the upper and lower margins of each box are the IQR, whiskers are maximum and minimum values, and dots and asterisks represent the number of patient with outlier data

and changes in cardiac index were found to be significantly improved in the intralipid group, detected during ICU stay measurements.

Conclusions

This study showed the benefits of infusion of 1.5 ml/kg of intralipid for 1 h after sternotomy, in preconditioning during off pump artery revascularization. Preconditioning with intralipid proved to decrease reperfusion injury in myocardium expressed by improvement in cardiac functions (EF and cardiac index) and normalization of cardiac markers (cardiac troponin I).

Abbreviations

CABG: Coronary artery bypass grafting; CK-MB: Cardiac-specific creatine kinase; CPB: Cardiopulmonary bypass; CTnI: Cardiac troponin I; CypD: Cychlophilin-D; EF: Ejection fraction; ERK: Extracellular signal regulating kinase; GSK-3β: Glycogen synthase kinase 3 β; ICU: Intensive care unit; mPTP: Mitochondrial permeability transition pore; OPCAB: Off pump coronary artery revascularization; PICCO: Pulsed induced contour cardiac output; TEE: Transeosophageal echo

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Authors' contributions

Dr. M.S.E: design of the work; literature search; provision of materials, patients, and resources; statistical expertise; critical revision of the article; and final approval of the article. Dr. S.M.A: analyzing and drafting the data; writing the article; provision of materials, patients, and resources; critical revision of the article; final approval of the article; and administrative, technical, or logistic support. Dr. M.E.: provision of materials, patients, and resources; analysis and interpretation; data collection; critical revision of the article; and final approval of the article. All authors have participated, read, and approved the manuscript.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research

committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The work was approved by the Ethics committee of Ain Shams University hospital (FMASU R 126/ 2020) on 15 December 2020.
All patients signed written informed consent before inclusion and explained the details of procedure.

Consent for publication
Consent for publication was obtained from all the participants.

Competing interests
The authors declare that they have no competing interests.

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