Original Article

# Pharmacological Preconditioning with Intralipid in Patients Undergoing Off-Pump Coronary Artery Bypass Surgery

**Gegal Pruthi, Naveen G Singh, P S Nagaraja, Rohini Mayur Balaji, N Manjunatha, P K Choudhary[1], Kurinchi Raja M**

*Department of Cardiac Anaesthesiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Jayanagar, [1]Department of Sports Medicine, Sports Authority of Karnataka, Bengaluru, Karnataka, India*

## Abstract

**Aims and Objectives:** The objective of the study was to determine the preconditioning myocardial protective effects of intralipid (IL) in off-pump coronary artery bypass (OPCAB) surgery by measuring highly sensitive troponin T (hsTnT) and cardiac-specific creatine kinase (CK-MB) as markers of myocardial injury. **Materials and Methods:** Thirty patients, scheduled to undergo elective OPCAB surgery, were randomly assigned to the IL group ($n$ = 15) or control (C) group ($n$ = 15); the IL group received an infusion of 20% IL 2 ml/kg, 30 min prior to revascularization and the control group received an equivalent volume of normal saline. Serum levels of hsTnT and CK-MB were measured before surgery and at 6 h, 24 h, 48 h, and 72 h postoperatively. Also, intraoperative hemodynamic parameters, inotrope use, ventilatory hours, ICU stay, postoperative left ventricular ejection fraction, postoperative lipid profile, renal and hepatic function tests were measured. **Results:** The hsTnT values at the 24 h, 48 h, and 72 h in IL group were significantly lower as compared with the control group. The decline in plasma levels of CK-MB mirrored the hsTnT levels post revascularization at 24 h and 48 h in the IL group compared with the control group; however, at 72 h, level was comparable in both the groups. None of the treated patients had abnormal lipid metabolism, deranged renal, and hepatic function. **Conclusion:** The study revealed Intralipid as a safe pharmacological preconditioning agent for OPCAB surgeries which can reduce the postischemic myocardial injury indicated by the reduction in postischemic cardiac enzymes hsTnT and CK-MB.

**Keywords:** *Cardiac specific creatine kinase, Intralipid, off pump coronary artery bypass*

## Introduction

Off-pump coronary artery bypass (OPCAB) surgery has been considered as a safe alternative to conventional on-pump coronary artery bypass (ONCAB) surgery. OPCAB has theoretical advantages in cardioprotection as it involves intermittent sequential short-term regional ischemic episodes compared with a longer global ischemic period caused by aortic cross-clamp during ONCAB.[1] Preserving myocardial function is one of the challenges faced by anesthesiologists during the management of OPCAB surgeries.

Myocardial protection includes various strategic interventions, which mitigate the extent of myocardial injury following not only an ischemic insult but also during the reperfusion period. To reduce the degree of myocardial injury during OPCAB surgery, a variety of mechanical (intracoronary shunts), pharmacological prophylaxis (beta blockers, calcium channel blockers, potassium channel openers, etc), and "conditioning" methods (ischemic and pharmacological agents like opioids and halogenated inhalational agents) are being used.[2] However, none of these modalities have been uniformly accepted.

At a cellular level of myocardial protection, mitochondria have been increasingly implicated in cell survival and apoptotic signalling during the ischemia reperfusion period. Particularly, the mitochondrial permeability transition pore (mPTP) has been suggested as the final effector.[3] Thus, targeting the mPTP opening has been considered to be a modality for cardioprotection.[4,5]

There has been upcoming literature in the recent times about the use of intralipid (IL) for myocardial protection. IL has been widely used as a component of parenteral nutrition, as a vehicle for different drugs such as propofol, and as a rescue therapy for local anesthetic overdose.[6] Recent



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***Address for correspondence:***
*Dr. P S Nagaraja, Department of Cardiac Anaesthesia, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru - 560 069, Karnataka, India.*
*E-mail: docnag10@gmail.com*

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available literature suggests that IL causes postconditioning by inhibiting the opening of mPTP channels and decreasing the myocardial infarct size.[7-9] However, there is limited data regarding the preconditioning effects of IL, if any, especially in OPCAB surgeries, which are devoid of traditional methods of cardioprotection with cardioplegia and hypothermia used in ONCAB surgeries.

Cardiac troponins have stood the test of time in predicting the extent of myocardial injury, particularly cardiac troponin T (cTnT), which has an excellent sensitivity (99%) and specificity (78%).[10]

The authors hypothesized that the cardioprotective effect of IL can be assessed by administering it to patients undergoing OPCAB surgeries, and determining the level of cardiac troponins and cardiac-specific creatine kinase (CK-MB) in the postoperative period.

## Materials and Methods

After obtaining the approval of the institutional ethical committee and informed written consent, thirty adult patients of either sex, aged upto 70 years, with multiple coronary artery disease scheduled for elective OPCAB surgery (performed by the same surgeon) with left ventricular ejection fraction (LVEF) >40% were enrolled for the study.

Patients aged above 70 years, combined valve and coronary surgery, ONCAB, redo cardiac surgery, hyperlipidemia, significant hepatic or renal dysfunction, uncontrolled hypertension, any disorder with immunological dysfunction (e.g., malignancy or positive serological test for HIV) in the last 6 months, preoperative treatment with nicorandil (an ATP-sensitive potassium channel opener), sulfonylurea (an ATP-sensitive potassium channel blocker), those who had a history of allergy to IL ingredients, that is, eggs and soya bean were excluded from the study.

The patients were randomized into two groups: IL group and control group (C group) based on closed envelope technique. Patients belonging to group IL ($n$ = 15) received 2 ml/kg 20% IL (Fresinius Kabi, Hombarg, Germany) and group C patients ($n$ = 15) received 2 ml/kg 0.9% normal saline 30 min prior to revascularization. The IL infusion was started slowly and was infused over a period of 30 min.

A baseline (T0) liver function test (LFT), renal function test (RFT), lipid profile, highly sensitive troponin T (hsTnT), and CK-MB were done for all the patients. Also, the baseline echocardiography and coronary angiogram reports were noted. Standard intraoperative monitoring included pulse oximetry, 5 lead electrocardiogram (ECG), nasopharyngeal temperature, capnography, central venous pressure monitoring, and invasive arterial pressure monitoring (after cannulation of internal jugular vein and femoral artery respectively). Post 3 min of preoxygenation, anesthesia was induced with fentanyl 4-5 mcg/kg, midazolam 0.05 mg/kg, titrated doses of propofol, and rocuronium 1 mg/kg. The trachea was intubated and normocapnic ventilation was established. Anesthesia was maintained with oxygen 50% in air, isoflurane of upto 0.5 MAC, 1 mcg/kg/h fentanyl, and intermittent bolus doses of rocuronium 0.25 mg/kg. Approximately 30 min prior to revascularization, group IL received 2 ml/kg IL 20% and group C received normal saline 0.9% in the same volume and for the same duration.

Hemodynamic parameters (heart rate and mean arterial pressure) were recorded at baseline (before initiation of IL or normal saline infusion), 5 min, 15 min, 30 min, 60 min, 120 min, and 180 min post initiation of IL or normal saline. Any requirement of inotrope intraoperatively and on postoperative day 1 (POD-1) was recorded as vasoactive inotropic score (VIS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 × epinephrine dose (mcg/kg/min) + 10 × milrinone dose (mcg/kg/min) +10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (mcg/kg/min).

Patients' trachea was extubated when they met the standard criteria of extubation. Ventilatory hours, LVEF at time of discharge, and duration of stay in the ICU were recorded for all the patients. Plasma hsTnT and CK-MB were analyzed at 6 h (T1), 24 h (T2), 48 h (T3), and 72 h (T4) postoperatively. Also, LFT, RFT, lipid profile levels were measured on POD-1.

### Outcomes

The primary outcome of the study was to evaluate the cardioprotective role of IL by assessing hsTnT and CK-MB postoperatively at 6 h (T1), 24 h (T2), 48 h (T3), and 72 h (T4).

### Secondary outcome measures

These included the following:

(1) Hemodynamic effect of IL on systemic circulation
(2) Clinical effect on inotropic use (intraoperatively and POD-1) and LVEF (at time of discharge)
(3) The serum levels of blood lipids (triglyceride and total cholesterol), serum creatinine, and total bilirubin
(4) Ventilatory hours and length of ICU stay were recorded
(5) All complications occurring during hospitalization including arrhythmias, stroke, infection, respiratory failure, hepatic or renal failure, reoperation, and mortality were noted.

### Statistical analysis

Data were expressed as mean ± SD. Comparisons between the groups were performed using independent Student's $t$-test for continuous variables that followed normal distribution. Mann-Whitney U test was used for non-normally distributed data. Chi-square or Fisher's test were used as appropriate for categorical variable comparisons between groups. Results were considered statistically significant at $P$ value ≤0.05.

**Table 1a: Baseline patient characteristics**

| Characteristics | IL group | C group | *P* |
|---|---|---|---|
| Age (years) (mean±SD) | 55.80±6.97 | 57.47±9.28 | 0.58 |
| Gender | M=15, F=0 | M=12, F=3 | 0.22 |
| Height (cms) (mean±SD) | 166.67±7.77 | 166.33±6.03 | 0.89 |
| Weight (kgs) (mean±SD) | 64.6±6.08 | 67.80±10.82 | 0.33 |
| Preoperative Beta blocker use | 13 | 14 | 0.54 |
| Co- morbid conditions | DM-9 | DM-10 | 0.70 |
| | HTN-7 | HTN-9 | 0.71 |
| LVEF (%) (preoperatively) (mean±SD) | 52.2±7.79 | 53±6.33 | 0.76 |
| Coronary artery disease | TVD=10 | TVD=13 | 0.39 |
| | DVD=5 | DVD=2 | |
| Baseline hsTnT (ng/ml) (median±IQR) | 0.02 (0.01-0.03) | 0.02 (0.01-0.03) | 0.90 |
| Baseline CK-MB (U/L) (mean±SD) | 22.27±12.83 | 20.4±11.48 | 0.68 |
| Baseline triglycerides (mgs/dl) (mean±SD) | 162.73±58.37 | 171.26±55.34 | 0.68 |
| Baseline cholesterol (mgs/dl) (mean±SD) | 136.46±32.97 | 140.33±29.31 | 0.74 |
| Baseline serum creatinine (mgs/dl) (mean±SD) | 1.01±0.18 | 1.00±0.25 | 0.85 |
| Baseline serum total bilirubin (mgs/dl) (median±IQR) | 0.60 (0.50-0.90) | 0.40 (0.40-0.58) | 0.04 |

TVD- triple vessel disease, DVD- double vessel disease, DM-Diabetes Mellitus, HTN- Hypertension

**Table 1b: Intraoperative patient data**

| Intraoperative | IL group | C group | *P* |
|---|---|---|---|
| Fentanyl used (mcgs) (mean±SD) | 490±63.25 | 520±84.09 | 0.28 |
| Volatile agent used (Minimum alveolar concentration used) (median±IQR) | 0.5 (0.43-0.50) | 0.5 (0.4-0.5) | 0.46 |
| VIS (mean±SD) | 3.53±2.36 | 3.13±1.25 | 0.56 |
| Number of Anastomosis (mean±SD) | 02.73±01.03 | 02.20±00.67 | 0.11 |

**Table 2a: Troponin *T* values postoperatively**

| Postoperative time | hsTnT values - IL group (ng/ml) | hsTnT values - C group (ng/ml) | *P* |
|---|---|---|---|
| T1 (6 h) (median±IQR) | 0.15 (0.07-0.29) | 0.31 (0.15-0.64) | 0.11 |
| T2 (24 h) (mean±SD) | 0.13±0.07 | 0.38±0.46 | 0.05 |
| T3 (48 h) (mean±SD) | 0.11±0.06 | 0.32±0.31 | 0.02 |
| T4 (72 h) (mean±SD) | 0.10±0.06 | 0.28±0.26 | 0.01 |

**Table 2b: CK-MB values postoperatively**

| Postoperative time | CK-MB levels ILgroup (U/L) | CK-MB levels C group (U/L) | *P* |
|---|---|---|---|
| T1 (6 h) (median±IQR) | 32.99 (21.40-50.82) | 43.16 (26.90-69.12) | 0.37 |
| T2 (24 h) (mean±SD) | 24.28±07.63 | 36.14±17.64 | 0.03 |
| T3 (48 h) (mean±SD) | 20.78±06.81 | 31.07±11.42 | 0.01 |
| T4 (72 h) (mean±SD) | 20.42±08.83 | 22.57±07.97 | 0.51 |

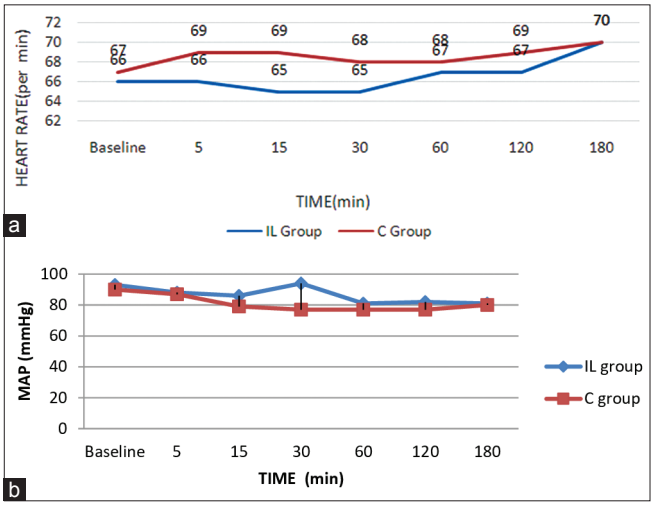


**Figure 1: (a) Intraoperative heart rate (HR) (per minute) after initiation of infusion. (b) Intraoperative mean arterial pressure (MAP) (mmHg) after initiation of infusion**

Statistical analyses were performed using MedCalc software version 12.2.1.0 (Ostend, Belgium).

## Results

### Characteristics of the study population

Thirty patients who underwent OPCAB surgery were randomly assigned to either of the group (15 patients in each group).

Patients' baseline characteristics, preoperative investigations, intraoperative hemodynamics, and surgical data were comparable [Tables 1a, 1b and Figure 1a, b].

The hsTnT values at the 24 h, 48 h, and 72 h in the IL group were significantly lower as compared with the control group [Table 2a].

The decline in plasma levels of CK-MB mirrored the hsTnT levels post revascularization at 24 h and 48 h in

**Table 3: Postoperative patient data**

| Parameters | IL group | C group | *P* |
|---|---|---|---|
| Trigycerides (mgs/dl) (POD-1) (mean±SD) | 101.20±38.74 | 90.93±42.84 | 0.50 |
| Cholesterol (mgs/dl)(POD-1) (mean±SD) | 82.20±20.88 | 82.26±30.02 | 0.99 |
| Serum creatinine (mgs/dl) (POD-1) (mean±SD) | 0.89±00.23 | 0.97±00.35 | 0.50 |
| Serum total bilirubin POD-1 (mgs/dl) (median±IQR) | 0.70 (0.43-0.90) | 0.40 (0.30-0.60) | 0.07 |
| VIS (POD-1) (median±IQR) | 2.5 (0.0-3.0) | 1.5 (0.25-2.0) | 0.58 |
| LVEF at the time of discharge (mean±SD) | 52.5±6.88 | 51.57±7.29 | 0.73 |

the IL group compared with the control group; however, at 72 h, level was comparable in both the groups [Table 2b].

The serum lipid levels, RFT and LFT at POD-1 were comparable [Table 3]. The clinical outcomes - inotrope requirement (POD-1), LVEF (at the time of discharge), and ventilatory hours did not differ between the two groups.

ICU length of stay (in days) was significantly prolonged in the control group (3.78 ± 0.69) as compared with the IL group (3.14 ± 0.53) with *P* value = 0.01.

One patient in the IL group and 2 patients in the control group had an episode of new onset postoperative atrial fibrillation (POAF). One patient in both the groups had ST elevations post-revascularization. ST changes settled in the patient in IL group, whereas the patient in the control group was taken for redo surgery after intraaortic balloon pump (IABP) insertion. There was one mortality noted in each group.

## Discussion

Periods of ischemia during sequential coronary vascular occlusion during OPCAB surgery can result in ventricular dysfunction,[11,12] endothelial injury, and can initiate apoptosis leading to post-revascularization injury.[13,14] Ischemia and reperfusion injury results in calcium overload, oxidative stress, and adenine nucleotide depletion leading to mPTP opening and increased membrane permeability to small molecules, including protons. This results in uncoupling of cellular oxidative phosphorylation and causes ATP depletion, followed by apoptosis and necrosis. Targeting the mPTP opening has been considered as one of the modality for myocardial protection.[4,5]

IL, a fat emulsion has been shown to exert cardioprotective effects. However, the mechanism of this protection is not completely known. The proposed molecular mechanism for cardioprotection is inhibition of the opening of mPTP pore through glycogen synthase kinase-3β via PI3K/Akt/ERK pathway which in turn activates Akt/ ERK pathway resulting in inactivation of glycogen synthase kinase 3-beta (GSK-3ß).[8]

In the current clinical trial, the use of IL as a preconditioning agent during OPCAB surgery significantly declined hsTnT and CK-MB plasma levels at 24 h and 48 h compared with the control group post-revascularization. Also, it was observed that a single bolus dose of IL 2 ml/kg over 30 min causes no significant difference in hemodynamics, perioperative lipid metabolism, hepatic and renal function. The present study used 2 ml/kg 20% IL which is within the range of American Society of Regional Anesthesia and Pain Medicine for reversal of local anesthetic cardiotoxicity and certain drugs cardiotoxicity.[15]

Li *et al.* reported that IL inhibits the opening of mPTP channels and decreased the myocardial infarct size. They have also postulated a second mechanism of protection by showing a 10-fold increase in the expression of micro-RNAs (MiR122), which are protective against apoptosis in rats.[7]

Another study by Rahman *et al.* demonstrated the molecular mechanism of IL that is inhibition of the mPTP with phosphorylation of GSK-3ß. They have administered IL 20% at the onset of reperfusion which resulted in 70% reduction in infarct size in the *in vivo* rat model.[8]

More recently Zhou *et al.*[9] reported that postischemic administration of IL prior to aortic cross-unclamping on reperfusion injury, is protective which was assessed using the biomarkers of myocardial injury. The study was conducted on patients undergoing valve replacement surgery. They received 20% IL 2 ml/kg just 10 min prior to aortic cross-unclamping. The Troponin T and CK-MB values were significantly lower in the IL group when compared with the control group (*P* = 0.004).

The results from the present study is concordant with the findings of previous experimental studies;[7-9] however, the results are not in agreement with the study conducted by Hu *et al.* as they failed to prove IL's preconditioning/postconditioning effects.[16] Probable reason for different result could be due to different dose and timing used in their study.

The appearance of biochemical markers Troponin T and CK-MB into the circulation are specific to myocardial tissue injury.[17] In the present study, the significant decline in plasma hsTnT and CK-MB levels 24 h and 48 h post-revascularization after administering IL 20% in OPCAB surgery patients is indicative of reduced myocardial cellular injury.

The limitation of the present study is that, the exact dose, the exact timing before revascularization, and the exact duration of IL infusion over which it has to be administered

still needs to be determined and studied over further clinical studies.

Thus, in conclusion, the study revealed IL, a safe pharmacological preconditioning agent for OPCAB surgeries, can reduce the postischemic myocardial injury indicated by the reduction in postischemic cardiac enzymes hsTnT and CK-MB.

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**Conflicts of interest**

There are no conflicts of interest.

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