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Propofol versus insulin cardioplegia in valvular heart surgeries assessed by myocardial histopathology and troponin I

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ABSTRACT

Background and Aims: Despite of the effectiveness of on pump cardiac surgeries in valvular diseases, cardioplegic arrest and myocardial reperfusion injury are still an obstacle. Many cardioprotective additives are tried but the obtained laboratory results are mixed. Our objective was to compare the effects of supplementing the cardioplegia solution with propofol or insulin evaluated not only by laboratory biomarkers but also with papillary muscle biopsy in patients undergoing on pump valvular surgeries.

Methods: Sixty adult patients were randomly assigned into three equal groups to receive: cold blood cadioplegia (control (C) group), supplemented with either 9 mg/L propofol 10% (P group), or 10 IU/L regular insulin (I group)

Results: Propofol induced significant higher myocardial protection presented by better histopathological grading of the obtained muscle biopsies when compared to either group C (P = 0.0460) or group I (P = 0.014), lower postoperative dysrhythmia (P = 0.004), lower troponin I release (40.57 ± 8.5 vs 47.7 ± 6.22-fold increase), and more eukalemic state with lower need for K supplementation than insulin.

Conclusion: Propofol was superior to insulin in providing higher grade of myocardial protection with lower troponin I release, more steady K level and lower postoperative complications.

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KEYWORDS
Propofol; insulin; cardioplegia; valvular surgery

1. Introduction

Although the usefulness of cardioplegia solution to arrest the heart during cardiac surgery with cardiopulmonary bypass (CPB), different degrees of myocardial damage and dysfunction can occur as a result of ischemia and disruption of metabolic and ionic homeostasis [1]. During ischemia, anaerobic metabolism leads to formation and accumulation of lactic acid (intracellular acidosis), which consequently elevate the concentration of intracellular sodium. The later can cause osmotic swelling and damage of sarcolemma of the cells. Moreover, prolonged ischemia can also lead to uncontrolled cellular calcium mobilization and formation of reactive oxygen species (ROS). Persistent elevation of intracellular calcium and the generation of ROS can destruct the integrity of mitochondrial cell membrane [2], disturb the electrical properties and contractility and eventually mitochondrial disruption with death of cardiomyocyte [3].

Further damage occurs during the reperfusion process due to reintroduction of oxygen free radicals into the previously partially injured ischemic tissue what is called ischemia/reperfusion (I/R) injury [4]. This myocardial damage lengthen the hospital stay, cause low cardiac output syndrome, stunning arrhythmias, necrosis and eventually delayed myocardial fibrosis [5]

Myocardial protection is an essential step during cardiac surgery. Different strategies and techniques have been evoluted in the last decades involve the integrity of the mitochondria and ionic transport [6], as modifications in composition, temperature, and routes of administration of cardioplegic solution (antegrade or retrograde) or cardioplegia enriched with pharmacological agents. Several drugs and anesthetic agents are implicated in accomplishing the cardioprotection . One of these is propofol which is a widely used intravenous anesthetic which can exert myocardium protection during oxidative stress and also reperfusion phase [7]. It exerts this through its antioxidant effect and lowering of lipid peroxidation [8]. Also, it produces significant inhibition of mitochondrial permeability transition pores (MPTP), scavenging of free radical and calcium channels inhibition [9] .

Another drug that has a positive contribution on postischemic myocardium is insulin. This is supported by the observation of increased mortality due to stress or even mild hyperglycemia accompanying myocardial infarction [10]. Exogenous insulin added to cardioplegia

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has been shown to reverse insulin resistance thus prevent lactate release, enhance glucose utilization by the myocardium and improve left ventricular work index. The beneficial effect of insulin extends to the reperfusion as it activates the pyruvate dehydrogenase which in turn stimulates aerobic metabolism [11]. Also, insulin is known to regulate the L-arginine nitric oxide pathway, thus induce vasodilation and reduction in the vascular resistance which improve the myocardial performance during reperfusion [12].

As the effectiveness of these two additives is still controversial, this study aimed to evaluate and compare the impact of cardioplegia supplementation with either propofol or insulin on myocardial protection for patients undergoing on pump valvular surgeries documented not only by laboratory tests and clinical objectives but also by punch biopsy of the left papillary muscle which is considered a good diagnostic tool of myocardial injury due to its early sensitivity correlated with the onset of ischemic cardioplegic arrest [13].

1.1. Primary outcomes

The primary outcome was myocardial injury assessed by the level of serum troponin I in blood samples collected preoperatively and at 12 h after surgery.

1.2. Secondary outcomes

- Myocardial ischemic stress evaluated by left papillary muscle biopsies.

-Systemic metabolic stress assessed by blood glucose level, serum K^+, the need for exogenous insulin or K^+, and renal function. Also, postoperative left ventricular ejection fraction, duration of weaning of mechanical ventilation, length of ICU stay, and postoperative morbidities (as acute myocardial infarction, dysrhythmia, the need of pacing, renal failure, and the use of acute hemodialysis).

2. Methods

2.1. Trial design and participants

This prospective, single-center, randomized, double-blind study was approved by the local ethics committee of Faculty of Medicine – Minia University, registered with Pan African Clinical Trial Registry (PACTR201710002696183) and carried out on 60 patients of both sexes in Minia University Hospital for cardiothoracic surgery between October 2015 and July 2017 in accordance with the Declaration of Helsinki and written, informed consents were obtained from all the patients before inclusion into the study.

Inclusion criteria included age between 18 and 60 years, elective on pump valvular surgery with first-time CPB. Exclusion criteria were refusal to participate, previous or emergency cardiac surgery, needing a redo operation, poor left ventricular function (EF <30%), combined CABAG and valvular surgery, diabetes mellitus, allergy to propofol, chronic renal failure, and severe preoperative comorbidities (e.g., sepsis, severe renal, or respiratory insufficiency)

2.2. Randomization and blinding

After eligibility for inclusion into the study was confirmed (Figure 1) and written informed consent was obtained, randomization was carried out using a computer generated tables and held in sealed envelopes by a staff member of the research team not involved in data collection or patient care and also was responsible for preparing the intervention materials immediately before use, wrapping them in an opaque bag and administer the intervention in a double blinded fashion (the participants, all the personnel in direct contact with them, and the histopathologist were blind to the study assignment).

2.3. Study intervention

The participants were randomly assigned into three groups of 20 patients each to receive either cold blood cardioplegia in a ratio of 4:1 blood-cardioplegia ratio (**control (C) group**), propofol-enhanced cold blood cardioplegia **(propofol (P) group)** where propofol of a final propofol concentration 9 µg/mL was supplemented or insulin-enhanced cold blood cardioplegia **(insulin (I) group)** where 10 IU/L of Humulin R (Eli Lilly Canada, Mississauga, Ontario, Canada) was added.

The composition of the used cardioplegic solution was 1 L of Ringer's lactate to which the following are added: 32 mmol magnesium sulfate (Memphis, Egypt), 10 mmol sodium bicarbonate 8.4% (Otsuka Pharmaceutical, Egypt), 20 mmol potassium chloride 15% (EPICO, Egypt), 100 mg lidocaine hydrochloride 20% (Pharmacell, Egypt), 2.4 mmol calcium gluconate 10%, and 13 ml glucose 25% .

The required propofol concentration (9 µg/mL) was prepared by diluting 1 ml of propofol 10% (10 mg) (Dongkook, South Korea) in 9 ml normal saline 0.9% (1 mg/ml) then 9 ml (9 mg/or 9000 µg) of the dilute was added to each one liter of cold blood cardioplegic solution.

2.4. Anesthetic management

All patients received preoperative physical examination, and recommended investigations. At the night of the surgery, the standard premedication lorazepam 1–3 mg and ranitidine hydrochloride 150 mg were administered. Prior to induction of anesthesia, a monitor with 5 lead ECG, end tidal CO_2, pulse-

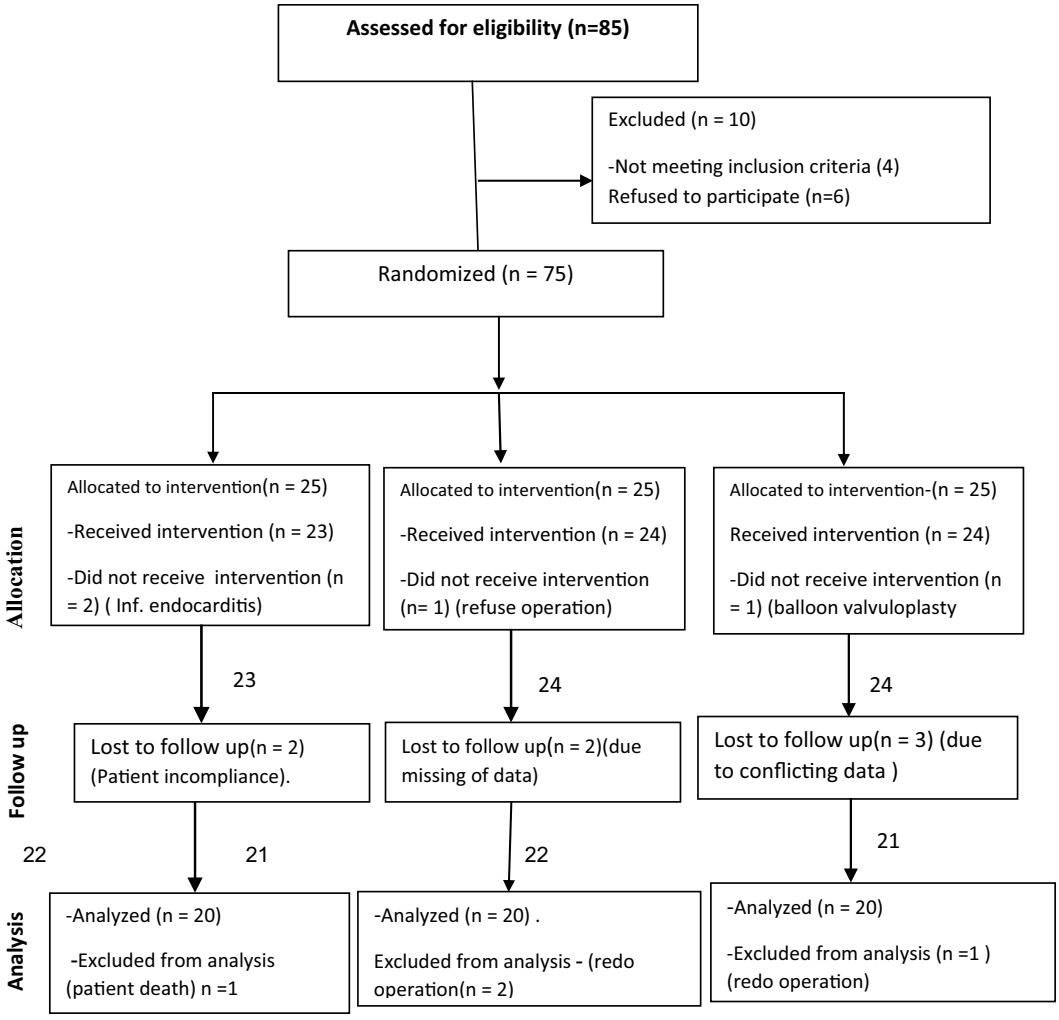


Figure 1. Consort flow diagram.

oximetry, and temperature (Philips Medizin System, Germany) was attached, a peripheral venous cannula was placed, and the patients were premedicated by 2.5 mg midazolam and baseline preoperative monitoring data were recorded. Under complete aseptic technique, radial artery cannulation was accomplished for ABG analysis and invasive blood pressure monitoring. After preoxygenation, anesthesia was induced by 1–2 mg/kg propofol 10%, 3–5 µg/kg fentanyl (Sunny Industry, USA) and 0.5 mg/kg atracurium (Glaxo Smith, Italy). After intubation, ventilation was adjusted to maintain end-tidal CO_2 between 35 and 40 mmHg. and 0.15 mg/kg atracuruim and sevoflurane were added for maintenance.

Also, a central venous line, an esophageal temperature probe, and urinary catheter were inserted after ensuring aseptic conditions.

Two additional doses of 100µ fentanyl were given, the first at skin incision and the other before sternotomy, cardiopulmonary bypass (CPB) was adjusted on non-pulsatile flow with a membrane oxygenator and the pump was primed by 1000 mL Ringer solution. Blood flow from the arterial pump was set at 2 L/min to keep mean arterial blood pressure between 50 and 70 mmHg. Hypotension during CPB was managed by direct alpha agonist (adrenaline), while hypertension was managed by vasodilators (nitroglycerine).

After aortic cross clamping, a roller pump drew oxygenated blood from the oxygenator and the cardioplegia solution was added in a 4:1 blood:cardioplegia ratio. Administration was done in antegrade manner through a needle placed between the aortic cannula and the aortic valve. Reloading was done every 20 min. The same surgical team performed all the included operations. First ventricular biopsy was taken by punchectomy (very minute in size) from left papillary muscle immediately after clamping and the second one from the same site just before declamping. It is necessary to clarify that all the studied patients were undergoing valve surgeries due to rheumatic valvular lesions. This type of lesion makes the papillary muscle amalgamated and adhesive to the affected valve which necessitate dissection of the attachment between the mc. and resected valve hence, the biopsy was obtained during this indispensable step. Samples were put in a formalin filled bottles, transported within 1 h after collection for histopathology examination by the same histopathologist who was blind to the group's assignment.

Before weaning from CPB, rewarming to 37°C and de-airing of the heart was done. Weaning from CPB was standardized guided by ECG and hemodynamic measurements and mechanical ventilation was resumed. Intubated patient was transferred to the ICU to be continuously supported by mechanical ventilation and fully monitored. Analgesia and sedation were administered as needed. When adequate spontaneous respiration with minimal oxygen requirements and stable heamodynamics are retained, extubation was permitted.

Any intra or post operative changes in blood glucose (beyond our strict protocol to maintain serum glucose between 5 and 10 mmol/L) or potassium level, were managed as follow: 25-g boluses of I.V. dextrose for hypoglycemia less than 5 mmol/L, 5–10-IU intravenous bolus of insulin for hyperglycemia more than 10 mmol/L or hyperkalemia above 6.0 mmol/L, and K^+ supplements for hypokalemia (K^+ <3.5 mmol). The need for insulin or K^+ was recorded and analyzed.

2.5. Histopathology assessment

Biopsies obtained from left papillary muscle were preserved in 10% formalin and embedded in paraffin taken for histopathological examination by H and E stain. Sections were cut and preserved in special container. Grades of injury [14] were classified as follows:

Grade 1 = normal appearance of myocardial muscle fibers;

Grade 2 = mild injury (up to one focus of damage), mild interstitial oedema and cytoplasmic infiltration;

Grade 3 = moderate oedema and distortion of muscle fibers (two or more foci of infiltrate of myocardial damage);

Grade 4 = diffuse severe oedema, perivascular hemorrhage, vasculitis with necrosis.

3. Statistic

3.1. Sample size

A Pilot study was performed before starting the research which revealed that the mean postoperative troponin level was 0.196 in group C, 0.094 in group P, and 0.134 in group I and SD within each group was 0.1, thus the number of patients required in each group was 20 patients to provide 80% power for one-way ANOVA test at the level of 5% significance using G Power 3.1 9.2 software.

3.2. Statistical analysis

- The collected data were analyzed using SPSS program (software version 20).

- For parametric quantitative data, descriptive statistics were done by mean + (SD) with minimum & maximum of the range but with number and percentage for categorical data. To compare the three groups, one-way ANOVA test followed by post hoc Tukey correction between each two groups were applied.

- For non-parametric quantitative data, Kruskal–Wallis test was used to compare the three groups followed by Mann–Whitney test between each two groups.

- Analyses within each group were done by paired *t*-test, for parametric quantitative data and for qualitative data by Wilcoxon signed rank test. Analyses were done for qualitative data using Fisher Exact test.

- The level of significance was taken at (*P* value < 0.05).

4. Results

Table 1 shows the demographic and operative data which was comparable between the three groups. Despite the randomized nature of the research, a significantly higher no. of patients with severe

Table 1. Demographic and operative data.

Variable	Group C (n = 20)	Group P (n = 20)	Group I (n = 20)	*P* value
Age (y)				
Mean ± SD	35.1 ± 7.97	39.15 ± 9.45	36.85 ± 8.21	0.332
Sex				
Male	10(50%)	8(40%)	8(40%)	0.847
Female	10(50%)	12(60%)	12(60%)	
Weight (kg)				
Mean ± SD	83.45 ± 9.9	78.5 ± 10.96	75.9 ± 14.26	0.133
Height (cm)				
Mean ± SD	166.8 ± 4.91	162.55 ± 8.23	165.55 ± 7.61	0.157
Aortic cross clamping time (min)				
Mean ± SD	53.15 ± 14.96	51.1 ± 15.38	58.15 ± 15.58	0.333
Cardioplegia volume (ml)				
Mean ± SD	750 ± 256.49	675 ± 244.68	775 ± 255.21	0.432
CPB duration(min)				
Mean ± SD	70.95 ± 17.96	70.1 ± 16.72	73.8 ± 16.22	0.772
Need for pacing (% of pt.)				
No	16(80%)	17(85%)	20(100%)	0.144
Yes	4(20%)	3(15%)	0(0%)	

No significant difference among studied groups (*P* value >0.05) – data presented as mean ± SD or %.

pulmonary artery pressure (PAP) was recorded in group (12 patients) and in group (8 patients). Also, there was a significant difference between C and I groups in preoperative ECHO, but the three groups were comparable in the postoperative one (Table 2).

- The changes in blood glucose was statistically insignificant between the three groups. However, in group (C) a significant elevation at 20 min after CPB (130.4 ± 27.22) and significant lowering at 48 h postoperatively (101.7 ± 13.29) were recorded in comparison to the preoperative values (114.15 ± 11.74). Thus, the intraoperative insulin need was significantly higher in group (C) (*P*- value = 0.001) (Figure 2).

- As shown in Figure 3, a significant higher serum K^+ values were recorded in group (C) compared to **(P)** at 20 min after CPB (*P* value = 0.023) and postoperatively at 6, 24 and 48 h (*P* = 0.021, 0.011 and 0.030, respectively). Intragroup comparison detected a significant decrease at 20 min on CPB in the three groups compared with preoperative baseline, with concomitant significant higher intraoperative K^+ was needed in group C compared to group (P) (*P* = 0.031) to be followed by

Table 2. ECHO parameters.

Variable	Group C (*n* = 20)	Group P (*n* = 20)	Group I (*n* = 20)	*P* value
Preop. Echo			▲(p = 0.001)	**0.014***
Normal	0(0%)	0(0%)	1(5%)	
Right ventricular dilatation	15(75%)	10(50%)	10(50%)	
Left ventricular dilatation	0(0%)	3(15%)	2(10%)	
Biventricular dilatation	5(25%)	3(15%)	0(0%)	
Right ventricular hypertrophy	0(0%)	3(15%)	4(20%)	
Left ventricular hypertrophy	0(0%)	1(5%)	3(15%)	
Preop. PAP		†(*p* = 0.001)	▲(*p* = 0.003)	**<0.001***
Mild	11(55%)	0(0%)	4(20%)	
Moderate	9(45%)	8(40%)	8(40%)	
Severe	0(0%)	12(60%)	8(40%)	
Preop. EF				0.099
Mean ± SD	66.05 ± 4.91	61.1 ± 8.94	(63.9 ± 7.01	
Postop. EF				0.769
Range	60 ± 7.94	59.3 ± 8.02	58.15 ± 8.43	
Mean ± SD				

PAP = pulmonary artery pressure; EF = ejection fraction. *Significant difference among the studied group.
†Significant difference between C vs P. ▲significant difference between C vs I – data presented as mean ± SD or %.

Table 3. ICU data and incidence of complications.

Variable	Group C (*n* = 20)	Group P (*n* = 20)	Group I (*n* = 20)	*P*-value
Time of weaning of mechanical ventilation (h)		2.51 ± 1.03	2.9 ± 1.09	**<0.001**[a]
Mean ± SD	3.93 ± 0.91	†(*p* < **0.001**)	▲(*p* = **0.006**)	
ICU stay(days)				0.133
Mean ± SD	2.65 ± 0.48	2.3 ± 0.73	2.6 ± 0.5	
Complications:				
-Dysrhythmia	8	–†	5▲	0.004a
-Renal failure	–	–	–	–
- Myocardial infarction	–	–	–	–

aSignificant difference among the studied group ($p < 0.05$). †significant difference between C vs P.
▲significant difference between C vs I – data presented as mean ± SD or No.

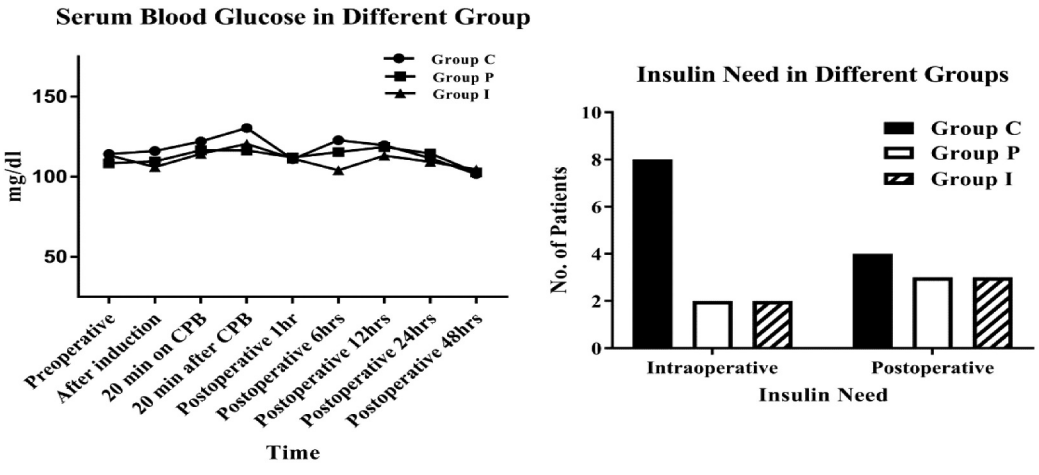


Figure 2. Blood glucose and insulin need.

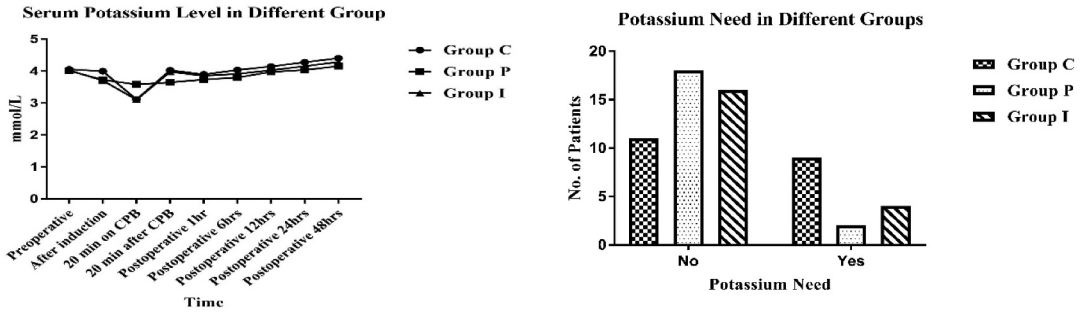


Figure 3. Serum K^+ level and K^+ supplementation.

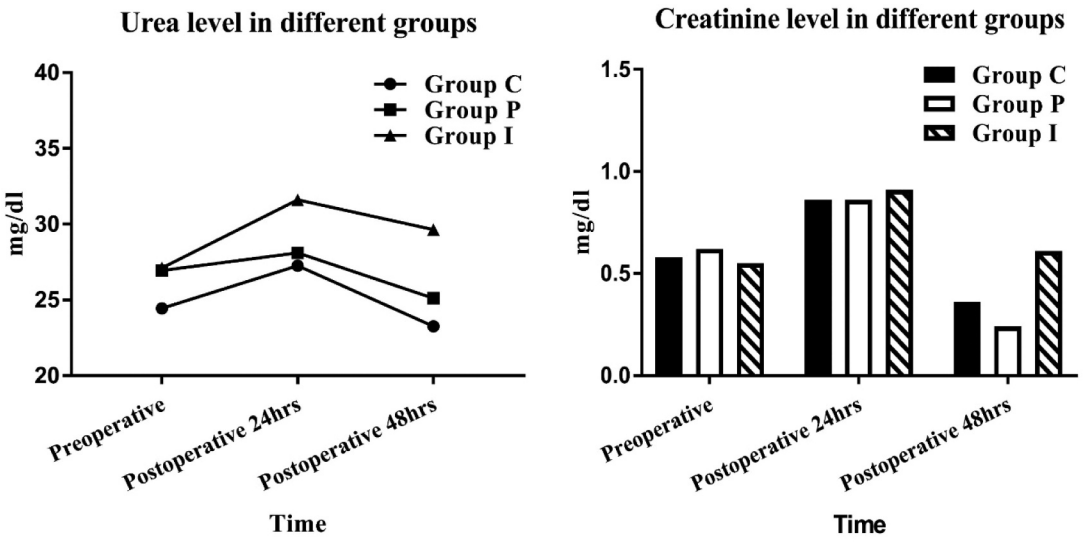


Figure 4. Urea and creatinine levels.

significant rise at 24 and 48 h postoperatively in group C and at 48 h only in group (I).

- The studied groups were comparable regarding the renal function. But intragroup comparison revealed postoperative significant increase at 24hrs. in serum creatinine in the three groups and in serum urea in group C only (Figure 4).

Also, ICU stay was insignificant among the three groups however, the time of weaning of mechanical ventilation was significantly longer (3.93 ± 0.91) and the number of patients suffered dysrhythmia was significantly higher (8 patients) in group C. in comparison to the other two therapeutic groups. No other complications were detected (Table 3).

As shown in table 4, group P offered more myocardial protection in the second ventricular biopsy with significantly higher number of patients (14 patients) (70%) detected in grade I (the best grade) followed by

Table 4. Histopathological changes in left papillary mc. biopsies.

Left ventricular biopsy	Group C (n = 20)	Group P (n = 20)	Group I (n = 20)	P value
First biopsy				
Grade I	20(100%)	20(100%)	20(100%)	–
Grade II	0(0%)	0(0%)	0(0%)	
Grade III	0(0%)	0(0%)	0(0%)	
Grade IV	0(0%)	0(0%)	0(0%)	
Second biopsy				
Grade I	7(35%)	14(70%)	8(40%)	**0.034**[a]
Grade II	6(30%)	3(15%)	8(40%)	
Grade III	0(0%)	2(10%)	0(0%)	
Grade IV	7(35%)	1(5%)	4(20%)	
		†(p = 0.014)	¥(P = 0.046)	
Grade I	7(35%)	14(70%)	8(40%)	0.057
	▲(P = 0.27)	†(P = 0.27)	¥(P = 0.27)	
Grade II	6(30%)	3(15%)	8(40%)	0.210
Grade III	0(0%)	2(10%)	0(0%)	0.126
Grade IV	7(35%)	1(5%)	4(20%)	0.060
	▲(P = 0.018)	†(P = 0.018)	¥(P = 0.018)	

[a]Significant difference among the study group (p < 0.05). †significant difference between C vs P. ▲Significant difference between C vs I. ¥Significant difference between P vs I – data presented as No. and %.

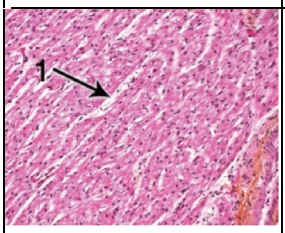
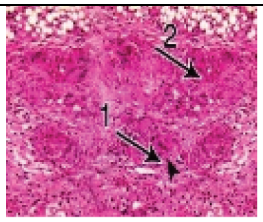
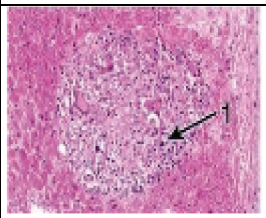
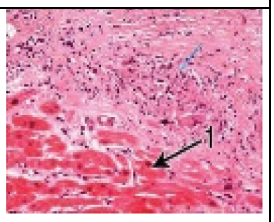
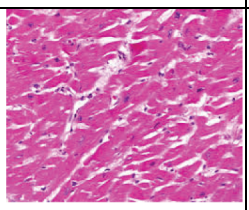
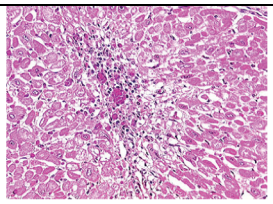
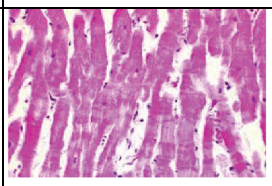
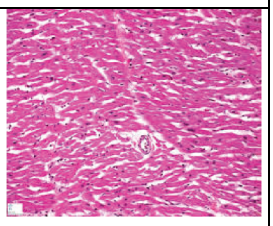
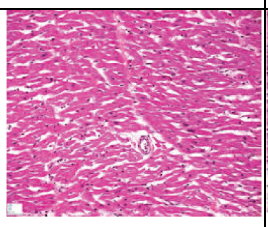
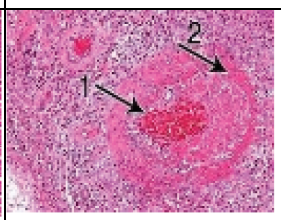
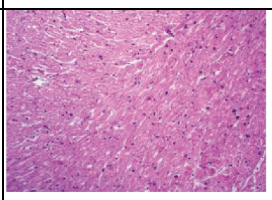
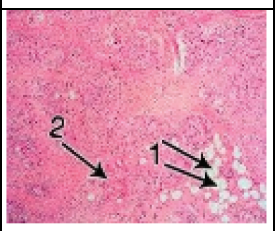
item	*Patient 1*		*Patient 2*	
Group **C**	Biopsy 1	*Biopsy 2*	Biopsy *1*	*Biopsy 2*
				
	1- Normal myocardial muscle fiber.	1-Sever interstitial oedema.2-Perivasculer capillary leak.	1- Norml myocardial muscle fiber.	*1- Severe peri vascular hemorrhage.*
Group **P**	Biopsy 1	Biopsy 2 .	Biopsy 1	*Biopsy 2*
				
	1- Normal myocardial muscle fiber.	*1*- Norml myocardial muscle fiber.	*1- Norml myocardial muscle fiber.*	*Normal* myocardial *muscle fiber.*
Group **I**	Biopsy 1	*Biopsy2*	Biopsy 1	*Biopsy 2*
				
	Norml myocardial muscle fiber.	*1Perivasculer hemorrhage. 2- Intersttisl oedema*	*Norml myocardial muscle fiber.*	*1,2 Celluler hydrophilic degeneration and massive oedema* *1-Mild interst. Oedema.*

Figure 5 Grades of myocardial biopsy in the studied groups.

Table 5. Changes in troponin I level and its correlation with histopathological grading of myocardial biopsy.

Troponin I	Group C (n = 20)	Group P (n = 20)	Group I (n = 20)	P value
Preoperative Mean ± SD	0.0104 ± 0.0005	0.0103 ± 0.0005	0.0102 ± 0.0004	–
Postoperative troponin Mean ± SD	0.82 ± 1.43# **P < 0.0001**	0.44 ± 0.95# **P < 0.001**	0.49 ± 0.62# **P < 0.001**	–
Postoperative -VE	0(0%)	0(0%)	0(0%)	0.134
+VE	20(100%)	20(100%)	20(100%	
Degree of increase Mean ± SD	77.33.±13.33	40.57 ± 8.5	47.7 ± 6.22	0.155
Correlation between serum troponin I and histopathological grading				
		R		*P* value
Group C	0.249	0.289		0.249
Group P	0.255	0.278		0.255
Group I	0.165	0.487		0.165

Significant difference within the group ($p < 0.05$). From 0 to 0.24: No correlation; From 0.25 to 0.49: poor correlation; From 0.5 to 0.74: fair correlation: From 0.75 to 1: strong correlation.

group I (8 patients) (40%) and lastly group C (7 patients) (35%) (P value = 0.034). Figure 5 shows demonstrative cases of lt. ventricular papillary mc. biopsies in the three studied groups. Cellular protection was evident in group P with preservation of cytoplasmic architecture while cellular injury were obvious in groups C and I that ranges from mild cytoplasmic oedema up to massive peri-vascular hemorrhage and hydrophilic degeneration.

-The changes in troponin I were statistically insignificant among the studied groups. However, intragroup analysis revealed variable degrees of positive elevation in the second sample within each one of the three groups relative to the preoperative values, as it was 77.33 folds in group C, 47.7 folds in group I and 40 folds in group P. Studying correlation between serum troponin I and degree of myocardial injury in each group revealed poor correlation ($r < 0.4$) (Table 5) .

5. Discussion

Myocardial dysfunction can occur during on pump cardiac procedures due to deficiency of oxygen and nutrient as a result of aortic cross clamping. Restoration of the flow can exert ischemia-–reperfusion (I/R) injury which if sustained induces injury to cardiomyocytes and coronary microcirculation, and eventually cell death. The cardioprotective drugs usually target to either inhibition of injurious activities, e.g., scavenging of ROS or enhancement of protective mechanisms as increased adenosine or nitric oxide formation [15]. Also, cold cardioplegia can offer some degree of myocardial protection by decreasing the oxygen demand during times of low flow [16].

Due to the raising number of patients requiring on pump valvular surgeries, this prospective randomized controlled trial attempted to assess the myocardial protective effect of cold blood cardioplegia enriched with propofol or 10 IU regular insulin. The results demonstrated that propofol group was superior to insulin and control groups in inducing more cytoplasmic and cellular myocardial protection against IRI evidenced by the histopathological architecture and grading of left papillary muscle biopsy, lower troponin I level at 12 h after surgery. Also, propofol showed more eukalemic state with less potassium supplementation, more euglycemic state and no incidence of arrythmias. Follow propofol in achieving these goals was insulin and lastly the control group.

In this research, standardized cardioprotective policies were utilized for all groups as cold blood cardioplegia and the use of cardioprotective volatile anesthetics for anesthesia. Many clinicians accustomed to deliver cold oxygenated blood as it offers buffering effect and a consistent myocardial blood flow [17].

On revision of previous studies, it stated that the use of a large dose of propofol during CPB can attenuate postoperative myocardial cellular damage [18]. Also, in another clinical trial which investigated the safety and efficacy of cardioplegia supplemented with 6 µg/mL propofol, the research designers themselves found that dose was low even than that routinely detected in the plasma during induction of cardiac anesthesia and justified this because propofol cardioplegia was not studied previously and their desire to avoid any hazardous to the participants. After study completion, they recommended the use of higher concentration [19]. Thus, 9 µg/mL was the selected dose to be studied in the current research.

Analysis of the demographic, operative, and the postoperative ECHO data showed comparability between the studied groups however, significant changes were recorded in the preoperative ECHO as all the recruited patients were having some degree of preoperative pulmonary artery hypertension either mild, moderate, or severe. Unintentionally and despite the randomization of the study, those had severe preoperative pulmonary hypertension were significantly higher (12 out of 20 patients (60%)) in propofol group. However, this was in interest and favor of our concluded results as despite of more patients who were suffering from cardiac problems in group P, yet it showed more myocardial protection than the other two groups .

As CPB induced hyperglycemia has deleterious effects on myocardium so, controlled serum glucose level is considered a cornerstone for myocardial protection. Diabetic patients were excluded from the current study to avoid bias during monitoring of serum glucose and a strict local protocol was followed to maintain serum glucose between 90 and 200 mg/dl. It was noticed that none of the patients suffered hypoglycemia conversely, eight cases (40%) in group C exceeded that cut-off value during the bypass and 20 min after CPB whom managed by 5–10 IU insulin repeated as needed until reaching our protocol range. Four of those patients (50%) had endured rapid atrial fibrillation (AF) resistant to loading amiodarone and DC shock was needed (360 Joules). On the other side, only 2 cases (10%) in both group P and I had gone hyperglycemia and responded simply to regular insulin.

Eequally important was serum K as dyskalemia is a common event in open cardiac surgeries. The current research showed hypokalemia on bypass in the three studied groups. Dilutional hypokalemia was incriminated due to the effect of priming fluid of CPB. Postoperatively, nine cases (45%) in group C need potassium supplementation at 1, 24 and 48 h postoperatively. Again four (45%) of these nine cases suffered rapid AF managed by DC shock (360 Joules). Two cases only (10%) in group P and 4 (20%) in group I were

in need for potassium correction at 1 h postoperatively without any other complications. These finding were matching with other trials as they reported more steady serum K in patients treated with insulin cardioplegia rather than control group [20].

Renal protection is mandatory in on pump cardiac surgery so renal function was assessed preoperatively and twice postoperatively (24 and 48 h). Our idea is that good myocardial protection will guarantee and offer renal protection rather than direct effect of the studied drugs due to their short half-lives. The three groups showed a significant rise in the postoperative serum creatinine in comparison to the preoperative value at 24 h, while postoperative serum urea showed significant increase only in group C. This mild elevation was temporary with no need for further nephrological interference or management. This rise may be caused by the postoperative hyperpyrexia state with protein catabolism and negative nitrogen balance .

Our results share the same experience with other investigators [19] who reported serum creatinine elevation by an average 7% in propofol enriched cardioplegia group in patients were undergoing aortic valve replacements (AVR) at 48 h. They could not attribute those differences occurred 48 h after surgery to propofol because of its short half-life and justified this finding by chance.

Cardiac troponins (hs-cTn) is a highly sensitive and specific biomarker for detection of myocardial injury which is inevitable in cardiac surgeries even those passed without perioperative complications and affected by surgical trauma, CPB, and the mode of myocardial protection [21]. In the current research, assessment of postoperative troponin I was done both qualitatively and quantitatively with the second follow up sample was withdrawn at 12 h after chest closure which coincide with high diagnostic sensitivity of troponin I elevation if occurred as serial sampling was not financially feasible. Qualitatively, postoperative troponin I values were positive in all participants while quantitative assessment highlights the link between pre and postoperative values and determine the degree of rise in each individual group. The highest degree of elevation was in Group C was with 77.33 folds rise relative to preoperative values while it was 47.74 folds in group I and the least degree in of rise was in group P (40 folds only) which confirms propofol ability to hinder troponin I release (even this was statistically insignificant) which in turn documenting its myocardial protective effect. In line with our findings, propofol cardioplegia induced 15% decrease in postoperative troponin T level in the treated group [19] and insulin cardioplegia exerted a decrease at 12 hours postoperatively in comparison to the control group [22].

Microscopic histopathological examination of left ventricular biopsies clarifies cellular protective effect of propofol followed by insulin on myocardium as group P recorded highest number of patients in grade I (14 cases – 70%) while group I in the next place with eight cases (40%) and group C in the last with 7 cases (35%). Grade I refers to normal muscle fiber architecture. There was poor correlation between serum troponin I and microscopic grading of myocardial injury in each group ($r < 0.4$) which can be explained by the inevitable troponin I release from the disrupted myocardial cell membrane caused by direct surgical trauma.

On contrary to ours, left ventricular biopsy could not detect any difference between those received the ordinary or insulin enriched cardioplegia but this can be attributed to the small number of biopsies (8 only) were investigated in that trial [20].

Lastly, this study has several limitations, as it targeted elective on pump valvular surgeries not urgent or combined with CABAG. Peak plasma concentration, half-life, and total clearance of the used doses of propofol and insulin were not investigated. Also, serial measurements of troponin I were not done due to financial obstacles.

6. Conclusions

This study suggests that both propofol and insulin supplementation in cardioplegia provided myocardial protection to various extents but propofol was superior to insulin evidenced by the ventricular biopsy and lower troponin I release. Also, it induced more steady K level and lower postoperative complications.

Disclosure statement

No conflict of interest.

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