Cardioprotective effect of ketamine-dexmeditomidine versus fentanyl-midazolam in open heart surgery in pediatrics: a randomized controlled double blinded study

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Received: 9 November 2022
Revised: 7 December 2022
Accepted: 24 December 2022
Published: 5 December 2023

The Egyptian Journal of Cardiothoracic Anesthesia 2023, 17:49–57

Background
Myocardial injury can occur during reperfusion of the heart during open heart surgery when the myocardium has been subjected to global ischemic cardioplegic arrest. The most common cardiac biomarker, cardiac troponin I (cTnI), can be used to assess the clinical prognosis of patients undergoing cardiac surgery. Anaesthetic medications have been linked to preventing ischaemia and reperfusion injury to the heart.
Methods
Eighty one children scheduled for open heart surgery were randomly divided into 3 groups Control group (C) (n=27): Isoflurane 1.2MAC was used to maintain anaesthesia Ketamine-dexmedetomidine group (n=27) KD Following the establishment of anaesthesia, dexmedetomidine (1 ug/kg) was administered over 10 minutes, followed by ketamine (2 mg/kg). maintenance throughout the operation was accomplished by administering ketamine (1 mg/kg/hr) and dexmedetomidine (0.5u g/kg/hr) while keeping variations in the mean arterial blood pressure to within 25% of the baseline. Fentanyl-midazolam group: (n=27) FM: Fentanyl (3 ug/kg) and midazolam (100 ug/kg over 2 to 3 minutes) were used to induce anaesthesia, and midazolam (1 ug/kg/min) and fentanyl (2u g/kg/h) were used to maintain anaesthesia during the procedure. a baseline sample for troponin was taken (T0), and measurements were made at declamping, 1hr, 6hrs, 12hrs, and 24hrs after declamping. heart rate (HR) and mean arterial pressure (MBP) readings taken at baseline, induction, at skin incision, 15, 30 min, post bypass at15, 30, 45, 60 min, duration of CPB and number of patients required inotropic support and nitroglycerine. extubation time and ICU stay were also recorded.
Results
Troponin level was significantly lower in the KD group at declamping, 1, 6, 12, and 24 hr after declamping compared to FM and C group ($P<0.001$). Extubation time was significantly lower in KD and FM groups compared to C group (P value <0.001) and was insignificantly different between KD and FM groups. ICU stay was significantly lower in the KD group compared to FM and C groups (P value <0.001).
Conclusion
By detecting the least increase in troponin I in paediatric patients undergoing elective congenital open heart surgery, the combination of ketamine and dexmeditomidine exerts great potential for cardiac protection and improving post-operative recovery compared to midazolam and fentanyl or the control group

Keywords:
Ischemic-reperfusion injury, troponin I, Dexmeditomidine, ketamine, midazolam

Egypt J Cardiothorac Anesth 17:49–57

1687-9090

Introduction

Congenital heart abnormalities are particularly difficult to treat since the child's heart is subjected to reduced myocardial function during the entire procedure. Furthermore, myocardial injury can occur during

Authors contributions: PFH conceived of the study, participated in the design of the study and participated in the data collection. AHS participated in the design of the study and drafted the manuscript and participated in the data collection. All authors read and approved the final manuscript.

The study was approved by the ethical committee of the faculty of medicine, Cairo University with approval number N-11-2022 and ClinicalTrials.gov registration number NCT05314569.

reperfusion of the heart during open heart surgery when the myocardium has been subjected to global ischemic cardioplegic arrest.

Neutrophils are activated by myocardial reperfusion injury, which sets off an inflammatory response that produces reactive oxygen species (ROS), cytokine release, and complement activation, all of which cause more heart injury. Cardiopulmonary bypass (CPB) during open heart surgery causes a large systemic inflammatory response in addition to the inflammatory response brought on by tissue reperfusion injury [1].

The issue of myocardial protection is crucial. The most common cardiac biomarker, cardiac troponin I (cTnI), can be used to assess the clinical prognosis of patients undergoing cardiac surgery [2].

Anesthetic medications have been linked to preventing ischemia and reperfusion injury to the heart. Although it does not affect neutrophil function, ketamine has been demonstrated to have anti-inflammatory properties and to lower endotoxin-stimulated IL6 production in human whole blood as well as neutrophils' production of ROS [3].

Dexmedetomidine is a central 2-adrenergic agonist with strong sympatholytic properties that is highly selective, short-acting, and potent. Due to its sedative/hypnotic and analgesic effects, which are augmented by its cardioprotective qualities, dexmedetomidine has been utilized as a component of general anesthesia, including cardiac surgical procedures [4].

After cardiac surgery, Riha and colleagues demonstrated that the combination of ketamine and dexmedetomidine had higher cardioprotective benefits as determined by cardiac markers when compared with sevoflurane-sufentanyl anesthesia [5].

It is well known that midazolam may have anti-inflammatory and antioxidant properties. It has been demonstrated that they have protective effects for people who have had heart surgery [6].

One opioid that shows a strong relationship with inflammatory mediators and myocardial protection is fentanyl. During cardiac surgery, it lessens the inflammatory reaction and ischemic reperfusion injury caused by CPB. These outcomes are linked to improved mobilization of intracellular Ca2+ and do not appear to be linked to neutrophil adherence in the coronary system [7].

To the best of our knowledge this is the first study comparing the combined effect of Ketamine-Dexmeditomidine (KD) versus fentanyl–midazolam (FM) against ischemia and reperfusion injury in pediatrics congenital heart surgery repair.

The aim of the study is to compare the combined effect of KD with FM as a cardiac protective tool against ischemia and reperfusion injury during cardiopulmonary bypass.

We hypnotized that KD combination would produce more protective effect than FM combination against cardiac ischemia and reperfusion injury during pediatric congenital heart surgery repair by measuring troponin I.

Patients and methods

After receiving approval from the institutional ethical committee with approval number N-11-2022 and ClinicalTrials.gov registration number NCT05314569, a prospective randomized double blinded trial was carried out. In the Abu El Reesh hospital at Cairo University, pediatric patients older than 6 months to younger than 24 months (the American Society of Anesthesiologists II and III), acyanotic heart diseases (VSD, AV canal, and partial anomalous pulmonary venous return(PAPVR)) were scheduled for elective open Congenital heart surgery using cardiopulmonary bypass. Parents' or guardians' written informed consents were obtained.

Patients who were less than 6 months old or older than 24 months, weighed less than 5 kg, had cyanotic heart disease, had heart failure, embedded a pacemaker, had pulmonary hypertension, received inotropic drugs prior to surgery, had a serum creatinine level greater than 1.5 mg/dl, had chronic liver disease, or were taking sulfonylurea, theophylline, or allopurinol were all excluded from the study.

A computer-generated random list was used to assign patients to study groups, which were then sealed in envelopes that could only be opened following study induction.

A complete blood count (CBC), coagulation profile, liver function tests, renal function tests, blood grouping, chest radiography, and recent echocardiography were all checked as part of the routine investigations after the anesthesiologist spoke with the guardians and confirmed fasting hours of 2 h for clear fluids and 6 h for solids.

20 min prior to induction, patients were premedicated intramuscularly with morphine sulphate 0.1 mg/kg and atropine (0.02 mg/kg). They were then brought into the operating room (OR), where they were placed on a warming mattress. All noninvasive monitors—including the electrocardiogram (ECG), the pulse oximeter, and the noninvasive blood pressure—were then attached, and the baseline heart rate and blood pressure were reported. In both groups, 3% sevoflurane was used to induce anesthesia, morphine (20 ug/kg) and then atracurium (0.5 mg/kg) was given to aid in endotracheal intubation and was infused intraoperatively (0.5 mg/kg/hr) as needed to maintain muscle relaxation.

The patients were then split into three equal groups based on the sort of medicine that had been injected. Anesthetists who were blind to the research groups prepared the medications.

Control group (C) (n=27): Isoflurane 1.2MAC was used to maintain anesthesia, keeping BIS between 40 and 60%.

Ketamine-dexmedetomidine group (n=27) KD

Following the establishment of anesthesia, dexmedetomidine (1 ug/kg) was administered over 10 min, followed by ketamine (2 mg/kg) maintaining between 40 and 60% of the bispectral index throughout the operation was accomplished by administering ketamine (1 mg/kg/hr) and dexmedetomidine (0.5 ug/kg/hr) while keeping variations in the mean arterial blood pressure to within 25% of the baseline.

Fentanyl-midazolam group: (n=27) FM

Fentanyl (3 ug/kg) and midazolam (100 ug/kg over 2 to 3 min) were used to induce anesthesia, and midazolam (1 ug/kg/min) and fentanyl (2 ug/kg/h) were used to maintain anesthesia during the procedure while keeping mean arterial blood pressure fluctuations within 25% of the baseline.

Patients in all groups were mechanically ventilated using a 1 : 1 oxygen to air mixture with the goal of keeping end tidal CO_2 at or below 35 mmHg.

A three-channel central venous line was placed. For invasive blood pressure monitoring an arterial line was put. To keep track of urine production, a urinary catheter was implanted. Two probes were used to measure the body temperature: one was placed in the nasopharynx to measure the core temperature and the other was placed on the big toe to measure the peripheral temperature. After induction, arterial blood gases were evaluated and repeated as necessary. For echocardiographic monitoring, a 7.5 MHz multiplane TEE probe and system (NC, USA) was used.

Fluid administration strategy was maintained by Ringer's lactate 10 ml/kg to keep CVP at 8 mmHg. When hemoglobin reached 8 g/dl, blood transfusion was initiated.

Heart rate (HR) and mean arterial pressure (MBP) were measured and recorded at baseline, before to anesthesia induction, as soon as the patient was intubated, at the time of skin incision, and then every 15 min for the first hour and then every 30 min until the surgery was complete. Number of patients who needed nitroglycerine and inotropic assistance during CPB were counted. Anesthetists who were blind to the specific medicines administered to ensure blindness of the recorded the data.

Hypotension was managed by intravenous fluid if not responding calcium gluconate 10% 1–2 mg/kg was given. Bradycardia was treated with atropine sulphate 0.02 mg/kg when heart rate was less than 25% of baseline. A bolus dosage of anesthetics (e.g., 1 ugkg1 dexmedetomidine in the KD group, 1 ugkg1 fentanyl in the FM group, and 10 ug/kg of morphine sulphate in the control group) was used to treat hypertension (MBP > 25% of basal value) or Tachycardia (HR > 25% of baseline), and nitroglycerine was injected if hypertension persisted.

A median sternotomy was done on all patients. Anticoagulation with heparin (300–400 IU/kg) was confirmed at an active clotting time (ACT) level that was at least three times the baseline level and at least 450 s. After using a nonpulsatile roller pump, a membrane oxygenator, and a conventional aorto-bicaval cannulation, CPB was started. Heparin is added to the priming solution, which also contains lactated Ringer's, in order to keep the hematocrit during CPB between 20 and 22%.

Throughout CPB, a moderate hypothermia of 26 to 28° was maintained. To stop the heart and sustain cardioprotection during aortic cross-clamp, cold blood cardioplegia (blood: crystalloid was 1 : 3 with K+ 30 mEq/l and $NaHCO_3$ 26 mmol/l) was given at a dose of 30 ml/kg, with top-up doses of 10 ml/kg given every 25–35 min.

After the repair was finished, the clamps were taken off, haemostasis was attained by administering protamine sulphate at a ratio of 1 mg/kg for every 100 IU/kg of heparin to reverse the heparin activity.

All anesthetics and muscle relaxants were discontinued once the surgery was finished. (0.1 mg/kg IM) of morphine sulphate was administered. The patient was then sent to the intensive care unit.

Elecsys Troponin I test, Hoffman Roche, which measures cardiac troponin I (cTnI), was used. Following induction, a baseline sample was taken (T0), and measurements were made at declamping, 1, 6, 12, and 24 h after declamping to look for signs of myocardial damage. Each sample was immediately centrifuged for 10 min at 3000 rpm before being examined.

The mean troponin level 6 h after aortic declamping was the main outcome.

Secondary outcomes included HR and MBP readings taken at baseline, induction, at skin incision, 15, 30 min, postbypass at15, 30, 45, 60 min, duration of CPB and number of patients required inotropic support and nitroglycerine. extubating time, pediatric intensive care unit length of stay were also recorded.

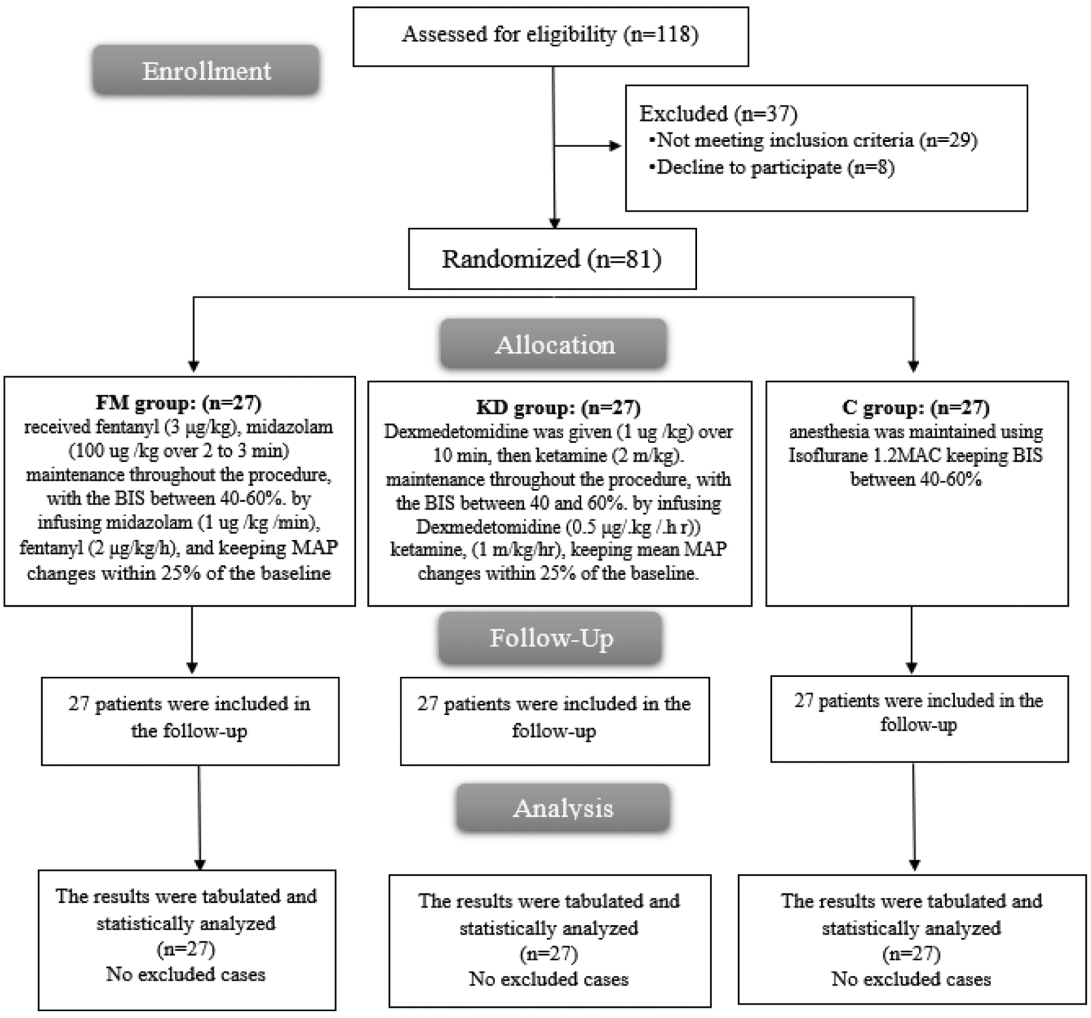
Sample size calculation

PASS 15 Power Analysis and Sample Size Software was used to calculate the sample size (2017). Kaysville, Utah, USA: NCSS, LLC; ncss.com/software/pass. The average 6 h postaortic declamping troponin level in the control group of a pilot trial on 6 children who underwent elective open repair of a congenital heart defect utilizing cardiopulmonary bypass was 22.33 ng/ml. The Tukey-Kramer (Pairwise) multiple comparison test with a significance level of 0.0500 has 80% power to detect a difference of at least 4.50 (20% difference) with a sample size of 72 individuals. A group's average standard deviation was taken to be 3.00. The number of envelopes was increased to 81 envelops assuming a 10% dropout rate (27 in each group).

Power analysis

SPSS v26 was utilized for the statistical analysis (IBM Inc., Chicago, IL, USA). Using the ANOVA (F) test, quantitative variables were given as mean and standard deviation (SD) and compared between the two groups.

Fig. 1



Consort flow diagram of the enrolled participants through each stage of the trial.

Table 1 Patient characteristics, duration of surgery and bypass time of the studied groups

	FM group (*n*=27)	KD group (*n*=27)	C group (*n*=27)	*P* value
Age (years)	11.22±5.47	12.19±5.27	10.63±5.45	0.567
Sex				
Male	13 (48.1%)	14 (51.9%)	15 (55.6%)	0.862
Female	14 (51.9%)	13 (48.1%)	12 (44.4%)	
Weight (Kg)	8.54±2.31	9.07±2.43	8.26±2.46	0.451
Type of surgery				
VSD	13 (48.1%)	12 (44.4%)	14 (51.9%)	
AVC	8 (29.6%)	8 (29.6%)	8 (29.6%)	0.975
PAPVR	6 (22.2%)	7 (25.9%)	5 (18.5%)	
Duration of surgery (h)	3.02±0.75	2.84±0.52	2.63±0.58	0.079
Bypass time (min)	54.6±33.31	51.67±18.61	40.37±14.2	0.070

Data are presented as mean±SD or frequency (%). AVC, atrioventricular canal; FM, fentanyl-midazolam; KD, ketamine-dexmedetomidine; PAPVR, partial anomalous pulmonary venous return; VSD, ventricular septal defect.

Table 2 Heart rate (beat/min) of the studied groups

	FM group (*n*=27)	KD group (*n*=27)	C group (*n*=27)	*P* value
Baseline	138.93±12.63	141.85±11.42	142.52±13.49	0.537
Induction	133.63±11.63	134.96±10	135.7±12.9	0.801
Incision	139.56±11.87	141.26±11.18	144.41±14.5	0.361
15 min	131.81±10.85	132.7±8.34	136.19±12.88	0.300
30 min	129.89±11	132±8.66	135.07±12.21	0.209
15 min postbypass	128.63±9.43	130.3±9.13	131.41±11.02	0.585
30 min postbypass	129±10.55	129.44±9.07	129.85±10.26	0.952
45 min postbypass	127.59±9.44	126.96±7.26	129.41±10.82	0.606
60 min postbypass	125.74±8.73	125.33±6.9	129.15±9.71	0.203

Data are presented as mean±SD, Data are presented as mean±SD or frequency (%). FM, fentanyl-midazolam; KD, ketamine-dexmedetomidine.

Table 3 Mean arterial blood pressure (mmHg) of the studied groups

	FM group (*n*=27)	KD group (*n*=27)	C group (*n*=27)	*P* value	
Baseline	62.78±12.1	65.3±10.47	64.59±11.42	0.703	
Induction	58.81±11.26	58.78±8.06	59.44±9.01	0.959	
Incision	63.59±11.09	65.33±10.5	65.19±9.72	0.795	
15 min	59.41±11.69	60.78±8.72	60.78±9.22	0.844	
30 min	59.37±10.77	60.85±7.76	60.26±10.4	0.854	
15 min postbypass	65.59±8.18	65.15±6.67	69.44±8.94	0.101	
30 min postbypass	64.85±7.49	64.89±6.28	69.37±9.28	0.055	
45 min postbypass	64.44±7.75	63.37±7.58	68.56±9.25	0.056	
					*P*1=0.481
60 min postbypass	62.63±7.54	60.07±7.88	67.52±8.82	**0.004***	*P*2=0.074
					P*3=0.003

Data are presented as mean±SD, Data are presented as mean±SD. FM, fentanyl-midazolam; KD, ketamine-dexmedetomidine. *P*1: *P* value between FM and KD groups. *P*2: *P* value between FM and C groups. *P*3: *P* value between KD and C groups. *: significant as *P* value less than or equal to 0.05.

The χ^2 test was used to examine qualitative data, which were reported as frequency and percentage (%). Statistical significance was defined as a two tailed *P* value less than 0.05.

Results

In this study 118 patients were assessed for eligibility. 29 people did not match the qualifying requirement and 8 patients refused to participate in the study. The remaining 81 patients were randomly allocated into three groups (27 patients in each). All allocated patients were followed-up and analyzed statistically. Fig. 1

Age, sex weight, type of defect, duration of surgery and bypass time were insignificantly different among the three groups. Table 1

Table 4 Inotropic agents, extubating time and ICU stay of the studied groups

	FM group (*n*=27)	KD group (*n*=27)	C group (*n*=27)	*P* value	
Inotropic agents					
Adrenaline	3 (11.11%)	9 (33.33%)	10 (37.04%)	0.068	
Milrinone	7 (25.93%)	8 (29.63%)	9 (33.33%)	0.837	
Dobutamine	10 (37.04%)	8 (29.63%)	8 (29.63%)	0.797	
None	0	2 (7.41%)	0	0.128	
					*P*1=0.080
Extubation time (hours)	51.11±28.55	36.89±15.94	89.78±25.43	<**0.001***	***P*2<0.001***
					P*3<0.001
					P1=0.002*
ICU stay (day)	4.1±1.09	3.05±0.67	5.24±1.14	<**0.001***	***P*2<0.001***
					P*3<0.001

Data are presented as mean±SD, Data are presented as mean±SD or frequency (%). FM, fentanyl-midazolam; ICU, intensive care unit; KD, ketamine-dexmedetomidine. *P*1: *P* value between FM and KD groups. *P*2: *P* value between FM and C groups. *P*3: *P* value between KD and C groups. *: significant as *P* value less than or equal to 0.05.

Table 5 Troponin level (ng/mL) of the studied groups

	FM group (*n*=27)	KD group (*n*=27)	C group (*n*=27)	*P* value	
At declamping	13.46±1.61	4.39±1.42	20.72±2.71		***P*1< 0.001***
				< **0.001***	***P*2< 0.001***
					P*3< 0.001
T1	17.18±±1.76	6.73±1.47	25.23±3.21		***P*1< 0.001***
				< **0.001***	***P*2< 0.001***
					P*3< 0.001
T6	14.53±1.47	4.52±1.55	22.45±2.65	< **0.001***	***P*1< 0.001***
					P*2< 0.001
					P*3< 0.001
					P*1< 0.001
T12	11.04±2.07	2.85±1.14	17.19±3.26	< **0.001***	***P*2< 0.001***
					P*3< 0.001
					P*1< 0.001
T24	9.32±1.91	1.47±0.72	12.58±2.95	< **0.001***	***P*2< 0.001***
					P*3< 0.001

Data are presented as mean±SD. FM, fentanyl-midazolam; KD, ketamine-dexmedetomidine. *P*1: *P* value between FM and KD groups. *P*2: *P* value between FM and C groups. *P*3: *P* value between KD and C groups. *: significant as *P* value less than or equal to 0.05.

Heart rate at baseline, induction, incision, 15, 30 min, postbypass at15, 30, 45, 60 min was insignificantly different among the three groups. Table 2.

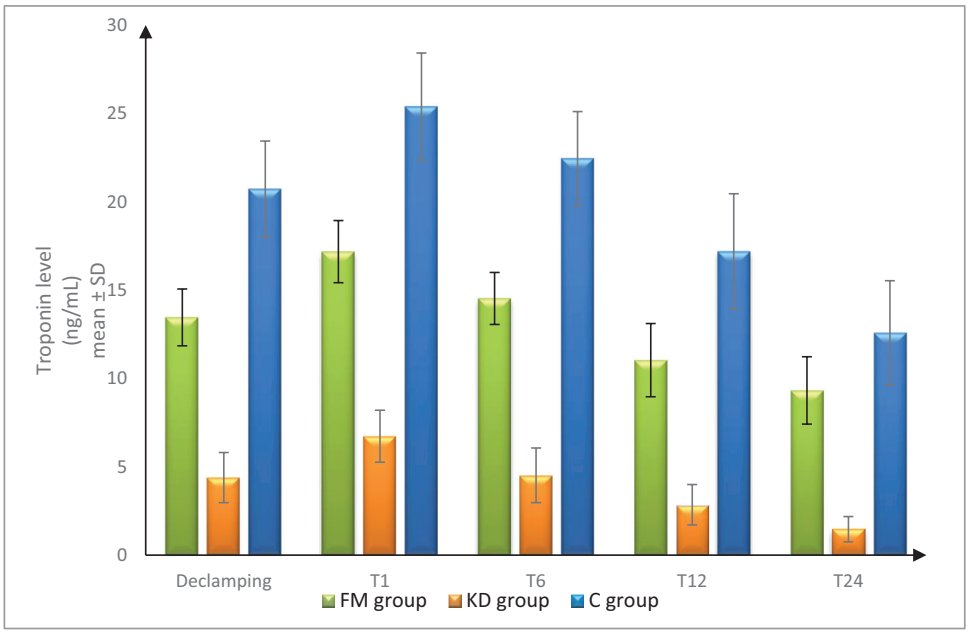
Mean arterial blood pressure at baseline, induction, incision, at 15, 30 min, postbypass at 15, 30, 45 min was insignificantly different among the three groups. MAP at 60 min postbypass was significantly lower in KD group compared with the C group (*P* value = 0.003) and was insignificantly different between FM and KD groups and FM and C group. Table 3.

Inotropic agents (Adrenaline, Milrinone, Dobutamine) were insignificantly different among the three groups. Extubating time was significantly lower in KD and FM groups compared with C group (*P* value < 0.001) and was insignificantly different between KD and FM groups. ICU stay was significantly lower in KD group compared with FM and C groups (*P* value < 0.001) and was significantly lower in FM group compared with C group (*P* value < 0.001). Table 4.

Troponin level at baseline was less 0.1 ng/ml in all patients. Troponin level was significantly lower in KD group at declamping, 1, 6, 12, 24 h after declamping compared with FM and C group (*P* < 0.001). Table 5. Fig. 2

The incidence of complications was insignificantly different among the three groups. Heart block occurred in 6 (22.22%) patients in FM group, in 7 (25.93%) patients in KD group and in 6 (22.22%) patients in group C. SVT occurred in 4 (14.81%) patients in FM group, in 2 (7.41%) patients in KD group and in 4 (14.81%) patients in C group. Residual VSD occurred in 2 (7.41%) patients in C group and did not occur in KD and FM groups. Table 6.

Fig. 2



Troponin level (ng/mL) of the studied groups.

Table 6 Incidence of complications in the studied groups

	FM group (*n*=27)	KD group (*n*=27)	C group (*n*=27)	*P* value
Heart block	6 (22.22%)	7 (25.93%)	6 (22.22%)	0.934
SVT	4 (14.81%)	2 (7.41%)	4 (14.81%)	0.633
Residual VSD	0	0	2 (7.41%)	0.128

Data are presented as frequency (%). FM, fentanyl-midazolam; KD, ketamine-dexmedetomidine; SVT, supraventricular tachycardia; VSD, ventricular septal defect.

Discussion

The current study showed a least rising at the level of troponin I with statistical significance difference in KD group at declamping, 1, 6, 12, and 24 h after declamping compared with FM and C group ($P < 0.001$).

As Cardiac surgery with the CPB procedure is associated with ischemia/reperfusion injury. Some techniques should be performed to prevent organ injury. The choice of anesthetic agent associated with better hemodynamic stability and relatively less cardiac injury may help in cardiac protection. In addition, the synergestic effect of combined drugs decrease the doses needed with less side effects.

Although racemic ketamine has been shown to inhibit ischemic preconditioning in vivo by blocking sarcolemmal adenosine triphosphate sensitive potassium ATP channels, it also reduced the inflammatory cytokine response associated with extracorporeal circulation compared with opioid-based analgesia, Welters and colleagues [8] but its sympathomimetic effects may lead to hypertension and tachycardia which may increase myocardial oxygen demand hence came the idea of adding dexmeditomidine as adjunct to ketamine. According to studies, dexmedetomidine protects the myocardium by raising the level of cAMP, which then causes a coronary vasodilatation effect. It has been demonstrated that preconditioning with dexmedetomidine activates prosurvival kinases to lessen cardiac ischemia/reperfusion injury Walters and colleagues, Ibacache and colleagues [8,9].

There were some disagreements regarding ketamine and cardiac output. While some scientists believed that ketamine directly depresses the myocardium, others claimed that it increases cardiac output indirectly by potentiating catecholamines Klockgether-Radke and colleagues [10]. Additional research showed that ketamine had positive direct ionotropic effects on human myocytes Hanouz and colleagues [11].

Dexmedetomidine was compared with various therapies in the context of cardiac surgery in 18 studies including 1730 patients; the majority of the data supported its myocardial protective effects in the adult population Wang and colleagues [12].

The creation of highly sensitive troponin assays made it possible to detect even tiny myocardial injuries and identify small-scale cardiac damage Neumann and colleagues [13].

According to Hegazy and colleagues study [14], adults patients assigned to the KD group had a significant drop in troponin T at 6 h after declamping, which is consistent with our findings.

In line with our findings, Riha and colleagues [5] found that patients receiving on-pump CABG surgery had lower troponin I levels in the early morning in the ketamine dexmeditomidine group than in the sevoflurane sufentanyl group. However, there were certain restrictions and contrasts between this study and ours. Adult patients participated in this observational retrospective investigation, and they measured cardiac biomarkers at different periods than we did.

Fentanyl is assumed to be selective for μ receptors; but it can also act with δ and κ receptors. Through δ receptor crosstalk with adenosine A1 receptors and mitochondrial K ATP linked mechanisms, Fentanyl preserves the heart against myocardial IR injuy Xu and colleagues [15].

It is well recognized that midazolam may have possible anti-inflammatory and antioxidant properties Leducq and colleagues [6]. It has been demonstrated that they have protective effects for patients who have undergone cardiac surgery Leducq and colleagues [6].

The generation of IL-1, tumour necrosis factor-alpha (TNF-), and IL-6 by murine phagocytes and their oxidative metabolism have been reported to be inhibited by benzodiazepines Zavala and colleagues [16]. A number of investigations have discovered that midazolam suppresses both the *in vitro* stimulation of human umbilical vein endothelial cells brought on by TNF- and human neutrophil activity Nishina and colleagues, Joo and colleagues [17,18].

Kim and colleagues [19] further discovered that midazolam exerted anti-inflammatory action by inhibiting inducible nitric oxide synthase and cyclooxygenase-2 expression, possibly through the suppression of NF-kappaB and p38 mitogen-activated protein kinase activation.

In our study there were no statistically significant difference in number of patients who required inotropic support across all groups however in FM group more patients required inotropic support than KD group with statistical significance coinciding with the results of Hegazy and colleagues [14] who found that lower number of patients required high dose inotropic support in KD group than fentanyl propofol group with significant difference.

In our study, hemodynamic variables (HR and MAP) were comparable in both ketamine-dexmeditomidine group and FM group. This goes in line with Petal and colleagues [20] who found no statistically significant differences in HR and MAP between the clonidine group, the clonidine and ketamine group and the control group. In contrary to our findings Hegazy and colleagues [14] found that MAP was higher in KD group than propofol fentanyl group the discrepancy with our study may be due to the use of propofol infusion for maintenance in fentanyl propofol group.

Regarding extubation time and ICU stay, Extubation time was significantly short in KD and FM groups compared with C group (P value < 0.001) and was insignificantly shorter in KD group than FM group. And ICU stay was significantly shorter in KD group than FM and C groups (P value < 0.001) and significantly reduced in KD group than FM group. These results coinciding with the findings of Riha and colleagues [5] and Hegazy and colleagues [14]. This could be related to the opioid sparing effect of dexmeditomidine which reduces anesthetics needs and causes less respiratory depression than fentanyl promoting early recovery and extubation Song and colleagues [21].

Also Dexmedetomidine was used in cardiac adult surgery by Gong and colleagues [22], who included a total of 8 randomized controlled studies. Their findings showed a lower risk of delirium, a shorter intubation time, but a higher incidence of bradycardia. However, due to the sympathomimetic impact of the additional ketamine, there was no bradycardia in our trial.

Our study had some limitations, first we did not measure postoperative troponin levels and determine the exact time reaching to baseline readings, second, we did not assess the sedative effect of dexmeditomidine and its impact on dissociative anesthetic effect of ketamine. Another limitation is the pain score and analgesic requirements were not investigated in this study. Finally, this is a single-center trial conducted in a very specific population.

We recommend the echocardiographic comparison of the groups could be useful for determining myocardial function after CPB.

Conclusion: By detecting the least increase in troponin I in pediatric patients undergoing elective congenital open heart surgery, the combination of ketamine and dexmeditomidine exerts great potential for cardiac protection and improving postoperative recovery compared with midazolam and fentanyl or the control group.

Acknowledgements
Funding: self -funded.

Ethics approval: Cardioprotective effect of KD versus FM in open heart surgery in pediatrics: A randomized controlled double blinded study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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