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Original Article

# Effectiveness of Dexmedetomidine as Myocardial Protector in Children With Classic Tetralogy of Fallot Having Corrective Surgery: A Randomized Controlled Trial

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*Objectives:* Efficacy of dexmedetomidine (DEX) as a cardioprotective agent in Indonesian children undergoing classic tetralogy of Fallot (TOF) repair with cardiopulmonary bypass (CPB).

*Design:* A prospective, parallel trial using block randomization along with double-blinded preparation of treatment agents by other parties.

*Setting:* National Cardiovascular Center Harapan Kita, Indonesia.

*Participants:* Sixty-six children with classic TOF scheduled for corrective surgery. No children were excluded. All patients had fulfilled the criteria for analysis.

*Interventions:* A total of 0.5 μg/kg bolus of DEX was added to the CPB priming solution, followed by 0.25 μg/kg/h maintenance during bypass. The placebo group used normal saline. Follow-ups were up to 30 days.

*Measurements and Main Results:* Troponin I was lower in the DEX group at 6 hours (30.48 ± 19.33 *v* 42.73 ± 27.16, p = 0.039) and 24 hours after CPB (8.89 ± 5.42 *v* 14.04 ± 11.17, p = 0.02). Within a similar timeframe, DEX successfully lowered interleukin-6 (p = 0.03; p = 0.035, respectively). Lactate was lower in the Dex group at 1, 6, and 24 hours after CPB ($p < 0.01$; p = 0.048; p = 0.035; respectively). Dexmedetomidine increased cardiac output and index from 6 hours after bypass, but vice versa in systemic vascular resistance. Reduction of vasoactive inotropic score was seen during intensive care unit monitoring in the Dex group (p = 0.049). Nevertheless, DEX did not significantly affect the length of ventilation (p = 0.313), intensive care unit stay (p = 0.087), and mortality ($p > 0.99$).

*Conclusions:* Dexmedetomidine during CPB is an effective cardioprotective agent in TOF children having surgery. Postoperative mortality was comparable across groups.



*Key Words:* cardiopulmonary bypass; corrective surgery; dexmedetomidine; interleukin-6; tetralogy of Fallot; troponin I

TETRALOGY OF FALLOT (TOF) is considered one of the most common cyanotic heart diseases, which corresponds to the prevalence of 5% to 10% of total cyanotic heart diseases.[1] Patients with TOF who underwent total repair have a better prognosis.[2] The use of cardiopulmonary bypass (CPB) provides a clearer view for surgeons to do open-heart surgery.[3]

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However, patients who undergo cardiac surgery supported by CPB experience inflammation, which could be caused by contact activation, ischemic reperfusion injury, and endotoxemia release. Reperfusion after CPB may lead to postischemic myocardial dysfunction, subsequently causing mitochondrial disruption and irreversible myocardial cell death.[4] This condition will inevitably release the specific biomarker associated with cardiac injury into the bloodstream.[5] Myocardial dysfunction may also indirectly trigger low cardiac output syndrome, which exacerbates systemic tissue hypoxia after CPB.[5] Suboptimal myocardial protection during TOF repair often happens due to the existence of pathologic right ventricular hypertrophy, which may worsen the mismatch between capillary supply and myocytes' demands.[6]

The mechanism involved in pharmacologic preconditioning and preconditioning using dexmedetomidine (DEX) during cyanotic TOF repair is not well established in humans. However, previous experimental studies showed that DEX had the capability to prevent extensive myocardial damage and suppress inflammation.[7-9] This study aims to ultimately investigate the efficacy of DEX in the pre- and per-conditioning phase as a myocardial protector in pediatric patients undergoing classic TOF total repair along with CPB support. The authors hypothesized that DEX alleviates postoperative myocardial injury and inflammation, proven by the reduction of troponin I, interleukin-6 (IL-6), and lactate in the bloodstream.[10] Additionally, the outcomes of cardiac conditioning were assessed using several variables, such as vasoactive inotropic score (VIS), systemic vascular resistance, cardiac output, and cardiac index. These parameters are rated in combination with the length of mechanical ventilation (MV) and intensive care unit length of stay (ICU LOS) as an indirect measurement of cardiorespiratory morbidities, as well as mortality.[11]

## Methods

### *Ethical Approval and Trial Registration*

This study was approved by the research ethical committee of Dr. Sardjito Regional Public Hospital/Faculty of Medicine Universitas Gadjah Mada (no. KE/FK/1267/EC/2022) and the institutional review board of the National Cardiovascular Center Harapan Kita (NCCHK; no. LB.02.01/XX.2/6179/2022). This study was also registered in the Clinicaltrial.gov Protocol Registration and Result System ID (no. NCT05579964).[12]

### *Study Design and Subjects*

This prospective, parallel, double-blinded, randomized controlled trial was conducted in the National Cardiovascular Center Harapan Kita, Indonesia. All children aged between 1 month to 18 years old with classic TOF scheduled for total corrective surgery were selected as recruitment candidates. Written informed consent was obtained from all children's guardians. The preoperative exclusion criteria consist of abnormal coagulation profile (international normalized ratio > 1.5), blood creatinine level >2 mg/dL, procalcitonin level >0.5 ng/mL, elevated liver transaminases >1.5 times compared to baseline, and nonelective surgery. The sample size was derived from a t test against mean differences from previous studies, explained thoroughly in the Statistical Analysis section. Based on the calculation, at least 66 children were eligible to be recruited in this trial. The recruitment process continued until the number of participants had reached the desired sample size. No changes to methods occurred after the commencement of the trial.

### *Intraoperative Monitoring and DEX Treatments*

Scheduled patients with TOF for elective surgery were first enrolled by attending physicians in the ward to assess for eligibility. Independent statisticians randomly assigned those eligible children into 2 groups with an allocation ratio equal to 1. Block randomization using well-shuffled, sealed envelopes was conducted throughout the process. In the intervention (DEX) group, a bolus of 0.5 μg/kg of DEX (*Precedex*) diluted in 5 ml of saline were administered into CPB priming solution, followed by administration of 0.25 μg/kg/h of DEX diluted in 20 mL of saline (NaCl 0.9% w/v) with infusion speed of 10 mL/h. In contrast, the placebo group was given physiological saline as a DEX substitute using the same methods as the intervention group. All interventions were done in the operating room. No additional DEX was given to patients as premedication before bypass. To ensure proper blinding toward caregivers and patients, both groups received identical syringes containing solution with the same appearance and volume, which were prepared by hospital pharmacists.

Following placement of monitors in the operating room, such as electrocardiogram, pulse oximetry, and peripheral venous access, both groups received fentanyl 3 to 5 μg/kg, midazolam (Sedacum) 0.1 mg/kg, and vecuronium (Ecron) 0.1 to 0.2 mg/kg as induction. All patients also underwent inhalation induction using sevoflurane 1 to 2 vol% in the mixture of oxygen and air. Endotracheal intubation was performed and maintained with pressure or volume control mechanical ventilation. After intubation, an invasive intra-arterial monitor and central venous catheter were placed, as well as a nasopharyngeal probe for temperature monitoring. Before the incision, a 2-μg/kg dose of fentanyl was added, followed by intermittent 0.02 to 0.05 mg/kg/h vecuronium injection and sevoflurane 1 to 2 vol% for anesthesia maintenance. Dexmedetomidine (in the intervention group) and saline (in the placebo group) were administered by an independent anesthesiologist into the priming solution and continued with infusion immediately after CPB until the end of CPB use. The operating team personnel and perioperative outcome assessors were all blinded to the patient's grouping information. No communication regarding trial intervention was established among patients, anesthesiologists, nurses, and pharmacists during perioperative and postoperative monitoring.

*Data Collection*

Venous blood samples were drawn from patients by trained nurses or phlebotomists within 5 minutes after induction (T1), 1 hour after CPB (T2), 6 hours after CPB (T3), and 24 hours after CPB (T4). Blood samples were collected in tubes with ethylenediaminetetraacetic acid preservative. Troponin I and IL-6 from the venous blood samples were measured using the enzyme-linked immunosorbent assay (human TNNI3/cTn-I; Elabscience and R&D System cat D6050, respectively). Manufacturers provided standards and controls to ensure proper kit calibration. Blood analyses were measured in the biomolecular laboratory at the research and development unit, NCCHK Hospital, Jakarta. Serum lactate was calculated using a blood gas analyzer (pHox Ultra Analyser, Nova Biomedical), of which the blood samples were derived from the arteries. Serial blood samples at T1, T2, T3, and T4, taken by trained nurses or phlebotomists, were sent directly to the NCCHK research lab for lactate measurement.

Additionally, postoperative hemodynamic performances, like cardiac output, cardiac index, and systemic vascular resistance, were measured using bedside transthoracic echocardiography (Phillips) at T1, T3, T4, and 48 hours after CPB (T5) by the attending cardiologist. Cardiac output was calculated by multiplying left ventricular stroke volume (obtained by multiplying the stroke distance/velocity-time integral, 0.785 as a constant, and square diameter of the left ventricular outflow tract through a parasternal long axis view) and heart rate. Dividing each patient's cardiac output to respective body surface area yields cardiac index. In contrast, systemic vascular resistance was measured by subtracting right atrial pressure (obtained via visualization of inferior vena cava's size and collapsibility) from mean arterial blood pressure, then divided by cardiac output.[13] The highest VIS data from postoperative medical records at T2, T3, and T4 were examined also. The VIS was calculated using a formula as follows: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10,000 × vasopressin dose (unit/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min).[14] The most used vasoactive-inotropic agents when coming off bypass were 2.5 to 10 μg/kg/min of dobutamine, 0.15 to 0.75 μg/kg/min of milrinone, or a combination of both, which were further adjusted based on the individual's hemodynamic status during intensive monitoring in the ICU. Occasionally, 0.05 to 0.1 μg/kg/min epinephrine or 0.025 to 0.5 μg/kg/min norepinephrine were used in combination with the aforementioned agents. The 30-day postoperative mortality, length of MV, ICU LOS, and postoperative pacing or complications were obtained from medical records. Age, sex, actual weight, height, body surface area, history of prematurity, past surgeries, and comorbidities were obtained from either presurgical history taking or medical records. Other data, such as duration of aortic cross-clamp, duration of surgery, duration of CPB, types of cardioplegia, measured right ventricular outflow tract gradient, and surgical procedures, were recorded during the surgery. No changes to trial outcomes happened after the commencement of the trial.

*Statistical Analysis*

Data analysis was planned before subject recruitment and was included in this protocol for ethical review. The sample size was determined using a two-tailed independent t-test against mean differences between 2 groups in terms of troponin I, as the primary outcome, from a previous study by Zhang et al. with a 95% CI and statistical power of 80%.[15] Unexpected dropouts were spared up to 10% of the sample size. Categorical data were presented as number of subjects and percentage and were compared using Pearson's $\chi^2$ test or Fisher's exact test as appropriate. Continuous or parametric data were presented as mean and SD; in contrast, nonparametric data were displayed as median and range. Assessment of the data distribution was done using Kolmogorov−Smirnov test. Longitudinal changes of the primary endpoint (troponin I) and several secondary endpoints, such as IL-6, lactate, cardiac output, cardiac index, and systemic vascular resistance, were assessed by the general linear model (repeated measures), followed by Bonferroni's adjustment method for multiple comparisons. The VIS, ICU LOS, length of MV, anthropometric, and other miscellaneous data were compared using an independent t-test (for parametric continuous data), Mann−Whitney U test (for nonparametric continuous data), or chi-square test or equivalent. Finally, the 30-day mortality was analyzed using chi-square test or equivalent. All statistical calculation was performed on the software SPSS Statistics version 29.0 (IBM SPSS, Inc, Armonk, NY). A p value of $< 0.05$ was deemed statistically significant.

## Results

Sixty-six subjects were recruited, beginning from October 2022 until April 2023, in this study who were divided equally between 2 groups. There was no excluded patient during the eligibility assessment, no patient lost to follow-up, and all patients' data were analyzed thoroughly (Fig 1). There were no statistically significant differences in patients' baseline characteristics across groups in terms of age, weight, body surface area, history of prematurity, comorbidities, history of previous surgery, CPB duration, aortic cross-clamp time length, baseline oxygen saturation, and duration of surgery (Table 1). All patients exhibited severe pulmonary stenosis with no significant difference in right ventricular outflow tract gradient between the 2 groups.

In the primary endpoint, as depicted in Fig 2, there was no statistically significant difference in the plasma level of troponin I between groups at the baseline ($0.14 \pm 0.04$ *v* $0.13 \pm 0.02$, $T_1$; $p = 0.345$). After bypass, there was a significant rise ($p < 0.05$) in blood troponin levels across all timeframes compared with the baseline ($T_1$) both in the Dex group and the placebo group. Notably, the plasma level of troponin I was lower in subjects who were given DEX compared with those in the placebo group at 6 hours after CPB ($30.48 \pm 19.33$ *v* $42.73 \pm 27.16$, respectively, at T3; $p = 0.039$) and 24 hours after CPB ($8.89 \pm 5.42$ *v* $14.04 \pm 11.17$, respectively, at T4; $p = 0.02$).

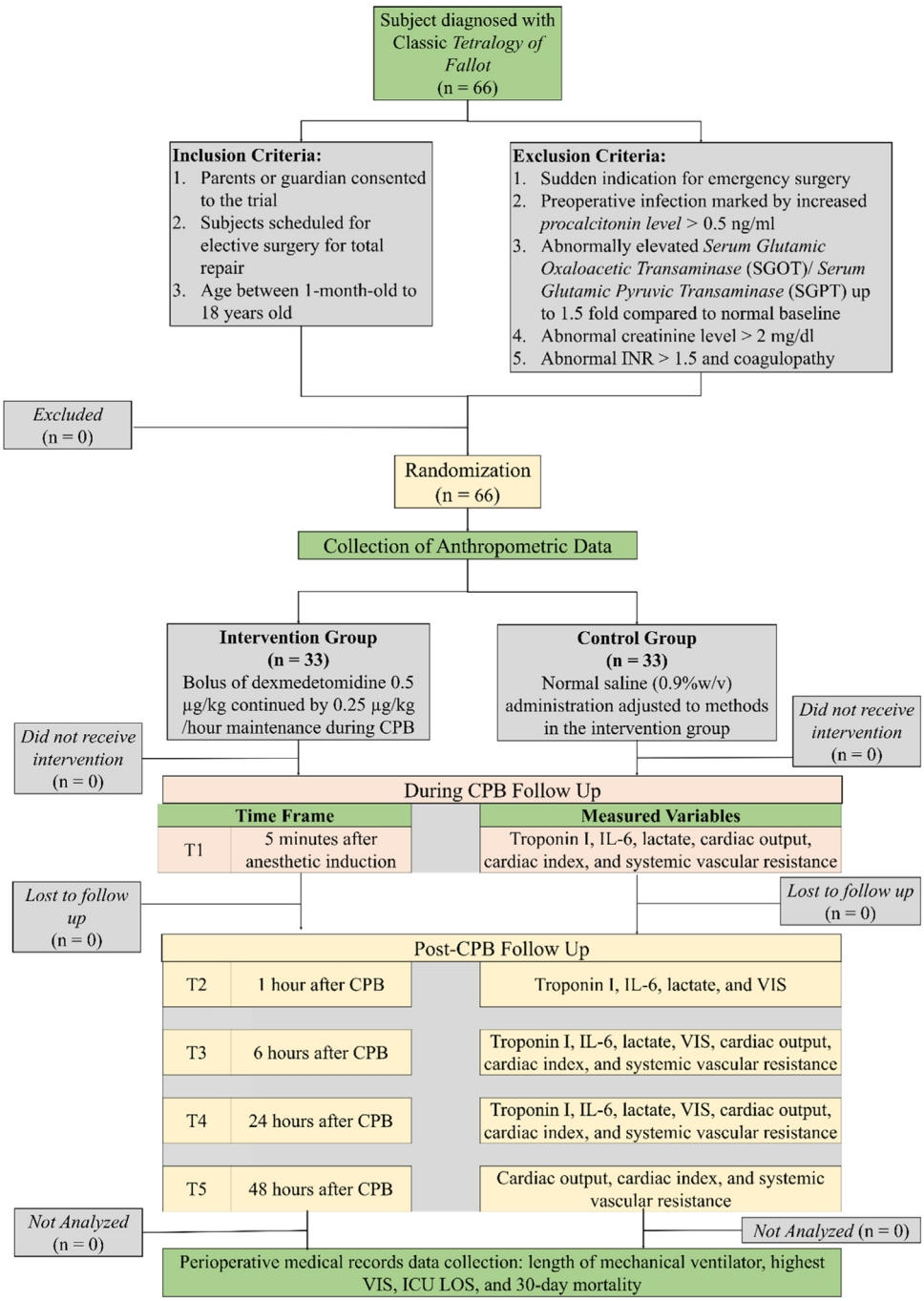


Fig 1. Flow chart of the study design and patient enrollment. CPB, cardiopulmonary bypass; ICU LOS, intensive care unit length of stay; INR, international normalized ratio; VIS, vasoactive inotropic score.

In Table 2, the plasma level of IL-6 was comparable between groups at the baseline (2.77 ± 0.9 *v* 2.71 ± 0.63, $T_1$; p = 0.781). After CPB, there was a rise in IL-6 level compared with the baseline across groups ($T_1$). At 6 and 24 hours after the surgery, plasma IL-6 level was lower in the Dex group as opposed to those in the placebo group (195.38 ± 112.29 *v* 263.19 ± 134.58, respectively, at T3 [p = 0.03]; 39.69 ± 18.5 *v* 49.42 ± 18.12, respectively, at T4; p = 0.035). Plasma lactate levels between groups at the baseline were similar (1.36 ± 0.39 *v* 1.36 ± 0.39, $T_1$; p > 0.99), yet there was an increase of lactate in relation to the baseline ($T_1$) across groups. Plasma lactate level was found lower in subjects who received DEX as priming solution and continuous infusion during CPB compared with those who received saline during CPB at 1 hour (1.44 ± 0.36 *v* 1.96 ± 0.7, $T_2$; p < 0.01), 6 hours (2.16 ± 0.86 *v* 2.56 ± 0.77, T3; p = 0.048), and 24 hours after CPB (1.58 ± 0.57 *v* 1.88 ± 0.56, T4; p = 0.035). Furthermore, increasing trends of cardiac output and cardiac index were found in both groups within several periods. Dexmedetomidine produced a dramatic increase in cardiac output starting from 6 hours after the end of the bypass, as did the cardiac index. Reciprocally, serial measurements of systemic vascular resistance suggested

Table 1
Baseline Characteristics of the Subjects

| | Dexmedetomidine (N = 33) | Placebo (N = 33) | Significance (p Value) |
|---|---|---|---|
| Age (mo), median (min-max) | 41 (9-174) | 41 (9-179) | 0.954‡ |
| Sex, n (%) | | | |
| Men | 20 (60.6%) | 15 (45.4%) | 0.218† |
| Women | 13 (39.4%) | 18 (54.6%) | |
| Body surface area (in $m^2$), median (min-max) | 0.53 (0.31-1.58) | 0.53 (0.34-1.39) | 0.832$ |
| Prematurity, n (%) | 3 (9%) | 1 (3%) | 0.613* |
| Other comorbidities, n (%) | 1 (3%) | 0 (0%) | 1.000* |
| History of previous surgery, n (%) | 5 (15%) | 5 (15%) | 1.000† |
| Baseline oxygen saturation (%), median (min-max) | 83 (55-98) | 83 (58-97) | 0.332‡ |
| Aortic cross-clamp time (in min), mean ± SD | 58.39 ± 18.65 | 57.94 ± 20.66 | 0.926 |
| Duration of CPB (in min), median (min-max) | 109 (51-200) | 101 (60-303) | 0.782‡ |
| Duration of surgery (in min), mean ± SD | 251.39 ± 63.89 | 236.61 ± 55.71 | 0.320 |
| Surgical procedure, n (%) | | | |
| Transannular patching | 20 (60.6%) | 25 (75.7%) | 0.186† |
| Valve-sparing | 13 (39.3%) | 8 (24.2%) | |
| Post-op pacing, n (%) | 27 (82%) | 21 (63.6%) | 0.095† |
| Types of cardioplegia, n (%) | | | |
| Crystalloid fluid | 28 (84.8%) | 30 (90.9%) | 0.708* |
| Fresh blood | 5 (15.2%) | 3 (9.1%) | |
| Pre-op RVOT gradient (in mmHg), median (min-max) | 76 (41-111) | 72 (60-111) | 0.969‡ |
| Post-op RVOT gradient (in mmHg), median (min-max) | 21 (8-80) | 19 (3-80) | 0.102‡ |
| Post-op Residual lesion, n (%) | | | |
| Ventricular septal defect | 3 (9%) | 2 (6%) | 1.000* |
| Pulmonary stenosis | 30 (90.9%) | 27 (81.8%) | 0.475* |
| Pulmonary regurgitation | 12 (36.4%) | 9 (27.3%) | 0.428† |

NOTE. All results are statistically analyzed using independent t-test, except for additional superscripted signs.
Abbreviations: CPB, cardiopulmonary bypass; RVOT, right ventricular outflow tract.
* Statistically analyzed using Fisher exact test.
† Statistically analyzed using chi-square test.
‡ Statistically analyzed using Mann-Whitney U test.

decreasing trends after the end of CPB. Moreover, DEX administration successfully lowered blood vessels' resistance at 6, 24, and 48 hours after bypass circulation. As a matter of fact, the highest value of VIS during ICU monitoring was significantly reduced after intraoperative DEX administration (8.75 *v* 10, p = 0.049) (Fig 3). The length of MV and ICU LOS did not exhibit significant disparity between groups (p = 0.313 and p = 0.087, respectively) (Fig 4). The results also suggested that the number of 30-day postoperative mortality has a null relationship with DEX administration (p > 0.99), as described in Table 2. There were 6 (n = 6) patients having stable postoperative atrioventricular block during monitoring. No harm or unintended effects, such as the development of shock, tachyarrhythmias, or anaphylactic reactions, were reported during the trial. Furthermore, no chemical or electrical cardioversion was done throughout the trial.

## Discussion

As the primary endpoint of the study, troponin I release was significantly lower in the Dex group compared with that of the placebo group within 6 hours after CPB separation (T3). The protective effect of DEX was also found in a study conducted by Ming et al., exhibiting significantly lower troponin I levels in the Dex group at 6 hours and 24 hours after surgery compared with that in the placebo group.[16] Additionally, as depicted in Fig 2**,** the highest troponin I level was achieved within 6 hours post−CPB separation (T3), which had been described as the late effect of reversible ischemia during open heart surgery. This phenomenon is known as "myocardial stunning." It happens when heart tissues' adenosine triphosphate is substantially depleted during CPB, which will release free radicals and hyper influx of calcium ions.[17] Furthermore, DEX during CPB reduced the side effect of myocardial stunning in this study, as shown by significantly different troponin I values between groups at the T3 time frame. There is a lack of biomedical explanation on how DEX provides cardiac protection in human subjects having TOF repair, but DEX was found to prevent postoperative myocardial reperfusion injury by cross-binding to α7n-AChR receptor, regulating intracellular calcium homeostasis, increasing nitric oxide production, and up-regulating AMPK/PI3K/Akt/eNOS pathway in the previous experimental studies.[7,18-21] This mechanistic process, including the generation of nitric oxide, may explain the lower troponin I release in the Dex group across timeframes. All these findings together concluded that the administration of DEX during CPB was found to improve the aftermaths of postoperative cardiac injury. However, mechanical procedures during classic TOF surgery, such as ventriculotomy or myocardial patching, may damage heart tissues regardless of the

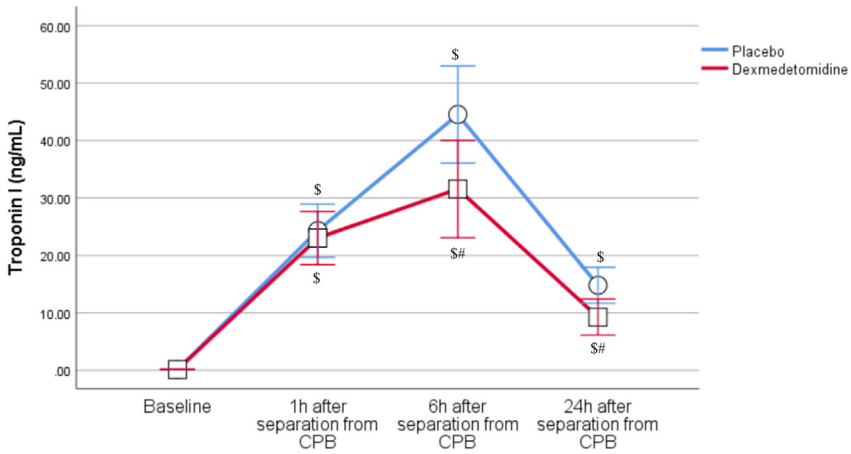


Fig 2. Plasma level of troponin I across timeframe. The error bar represents a 95% CI. CPB, cardiopulmonary bypass. *p < 0.05 compared with baseline; †p < 0.05 compared with placebo.

Table 2
Study Outcomes in Subjects between Dexmedetomidine and Placebo Group

| Outcomes | | Dexmedetomidine (N = 33) | Placebo (N = 33) | Significance (p Value) | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Primary endpoint | | | | | | |
| Troponin I (ng/mL) | | | | | | |
| 5 min after induction/baseline | T1 | 0.14 ± 0.04 | 0.13 ± 0.02 | 0.345 | −0.02 | 0.01 |
| 1 h after CPB separation | T2 | 23.56 ± 13.22 | 23.99 ± 12.30 | 0.891 | −5.85 | 6.71 |
| 6 h after CPB separation | T3 | 30.48 ± 19.33 | 42.73 ± 27.16 | 0.039* | 0.65 | 23.84 |
| 24 h after CPB separation | T4 | 8.89 ± 5.42 | 14.04 ± 11.17 | 0.020* | 0.83 | 9.46 |
| Secondary endpoints | | | | | | |
| Interleukin 6 (pg/mL) | | | | | | |
| 5 min after induction/baseline | T1 | 2.77 ± 0.90 | 2.71 ± 0.63 | 0.781 | −0.43 | 0.33 |
| 1 h after CPB separation | T2 | 173.12 ± 104.29 | 231.11 ± 143.14 | 0.065 | −3.59 | 119.58 |
| 6 h after CPB separation | T3 | 195.38 ± 112.29 | 263.19 ± 134.58 | 0.030* | 6.86 | 128.77 |
| 24 h after CPB separation | T4 | 39.69 ± 18.50 | 49.42 ± 18.12 | 0.035* | 0.73 | 18.74 |
| Lactate (mmol/L) | | | | | | |
| 5 min after induction/baseline | T1 | 1.36 ± 0.39 | 1.36 ± 0.39 | 1.000 | −0.19 | 0.19 |
| 1 h after CPB separation | T2 | 1.44 ± 0.36 | 1.96 ± 0.70 | < 0.001* | 0.24 | 0.79 |
| 6 h after CPB separation | T3 | 2.16 ± 0.86 | 2.56 ± 0.77 | 0.048* | 0.01 | 0.81 |
| 24 h after CPB separation | T4 | 1.58 ± 0.57 | 1.88 ± 0.56 | 0.035* | 0.02 | 0.58 |
| Cardiac output (L/min) | | | | | | |
| 5 min after induction/baseline | T1 | 1.23 ± 0.49 | 1.35 ± 0.54 | 0.376 | −0.14 | 0.37 |
| 6 h after CPB separation | T3 | 1.76 ± 0.62 | 1.42 ± 0.41 | 0.011* | −0.59 | −0.08 |
| 24 h after CPB separation | T4 | 1.99 ± 0.62 | 1.59 ± 0.44 | 0.003* | −0.67 | −0.14 |
| 48 h after CPB separation | T5 | 2.16 ± 0.69 | 1.71 ± 0.46 | 0.003* | −0.74 | −0.16 |
| Cardiac index (L/min/m$^2$ BSA) | | | | | | |
| 5 min after induction/baseline | T1 | 2.09 ± 0.81 | 2.34 ± 0.76 | 0.202 | −0.14 | 0.64 |
| 6 h after CPB separation | T3 | 2.85 ± 0.55 | 2.51 ± 0.68 | 0.032* | −0.64 | −0.03 |
| 24 h after CPB separation | T4 | 3.18 ± 0.36 | 2.79 ± 0.64 | 0.003* | −0.65 | −0.14 |
| 48 h after CPB separation | T5 | 3.30 ± 0.35 | 2.97 ± 0.64 | 0.012* | −0.58 | −0.08 |
| Systemic vascular resistance (dynes/s/cm$^{-5}$) | | | | | | |
| 5 min after induction/baseline | T1 | 3,354.03 ± 1,097.49 | 3,306.51 ± 970.47 | 0.853 | −557 | 461.96 |
| 6 h after CPB separation | T3 | 2,692.77 ± 860.93 | 3,108.57 ± 459.66 | 0.017* | 76.39 | 755.19 |
| 24 h after CPB separation | T4 | 2,292.93 ± 683.17 | 2,800.38 ± 667.99 | 0.003* | 175.17 | 839.72 |
| 48 h after CPB separation | T5 | 1,852.00 ± 663.45 | 2,201.34 ± 613.98 | 0.030* | 34.42 | 663.15 |
| 30-d mortality, n (%) | | 0 (0%) | 0 (0%) | 1.000† | | |

NOTE. All results are statistically analyzed using general linear model (repeated measures) except for those designated by a † sign.
Abbreviations: BSA, body surface area; CB, cardiopulmonary bypass.
* Statistically significant (p < 0.05) compared with placebo group.
† Statistically analyzed using Fisher exact test.

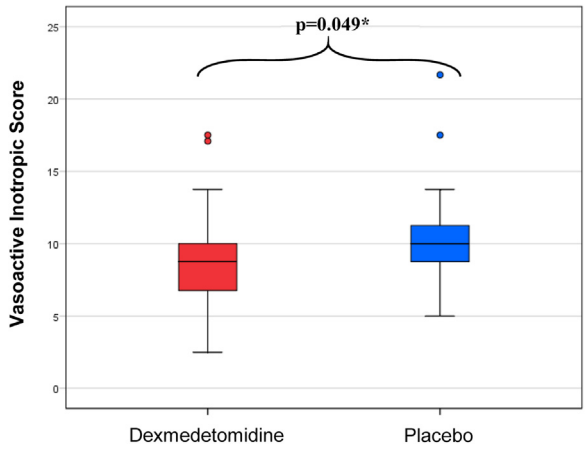


Fig 3. Comparison of vasoactive inotropic score between groups. The error bar represents a 95% CI. *p < 0.05 (statistically significant).

protective effect of DEX. Minute apoptosis and necrosis of cardiac cells occurred and released some of the troponin I that would be carried by blood at the end of CPB. This phenomenon explained the increased level of troponin in both groups within 1 hour after CPB separation (T2) compared with the baseline (T1).[22]

A previous study found that the patients with CPB-supported cardiac surgery presented a much higher 2-hour postoperative IL-6 concentration than those with CPB-supported nonsurgical cardiac procedures. This finding explained that early inflammatory reaction predominantly was caused by surgical trauma.[23,24] In secondary endpoints, IL-6 level in both groups was found to be significantly elevated starting 1 hour after CPB separation (T2) compared with baseline (T1), suggesting that inflammation by surgical trauma may not directly be ameliorated by DEX.[23,24] Myocardial ischemia and reperfusion injury, however, play a role in the late postoperative production of IL-6, as the level of IL-6 did not reach its peak immediately after surgery.[25] This is when DEX infusion successfully lowers a meaningful amount of circulated IL-6 compared with administration of placebo at 6 hours after CPB separation (T3), which corresponded with the result published by Abdelrahman et al.[26] In experimental studies, 1 biological mechanism of DEX in minimizing reperfusion injury was through down-regulation of HMGB1-TLR4-MyD88-NFkB signaling, subsequently inhibits the expression of IL-6 messenger RNA.[10,27]

Dexmedetomidine is known to reduce systemic lactate production through regulation of postoperative stress response and metabolic rate, which corresponded to the lower amount of blood lactate compared with saline-only administration, starting from 1 hour after CPB separation (T2) (Table 2).[28] It was noted in this study that the end of CPB use indicated the end of DEX infusion. However, stress and recovery constantly happened after surgery, which is correlated with high metabolic demand but may not be supplied adequately by the repaired heart. This phenomenon is called late-onset hyperlactatemia, which is a glycolytic stress response that eventually leads to the production of lactate without having hypoxia as its main cause.[29] Because DEX has a half-time elimination of 2 to 3 hours, its effect started to diminish from 6 hours after CPB when there was still ongoing lactate production.[30] This explained that the lactate level in both groups rose dramatically at 6 hours after CPB separation (T3) compared with the baseline (T1).

From these findings, there was a meaningful improvement of cardiac output and cardiac index in the Dex group compared with that of the placebo group starting from 1 hour after CPB separation, which was similar to the value of postoperative cardiac performance after DEX treatment during surgery by Tosun et al.[31] Low cardiac output syndrome, which is defined as a transient decrease of systemic perfusion due to myocardial dysfunction, was not found in the Dex group of this study. Supported by data from previous studies, DEX could cause low blood pressure and heart rate, yet it did not degrade cardiac output.[32,33] Additionally, the postoperative uptrends of cardiac performance after being treated with DEX had an inverse association with systemic vascular resistance. Lower systemic vascular resistance may have contributed to the

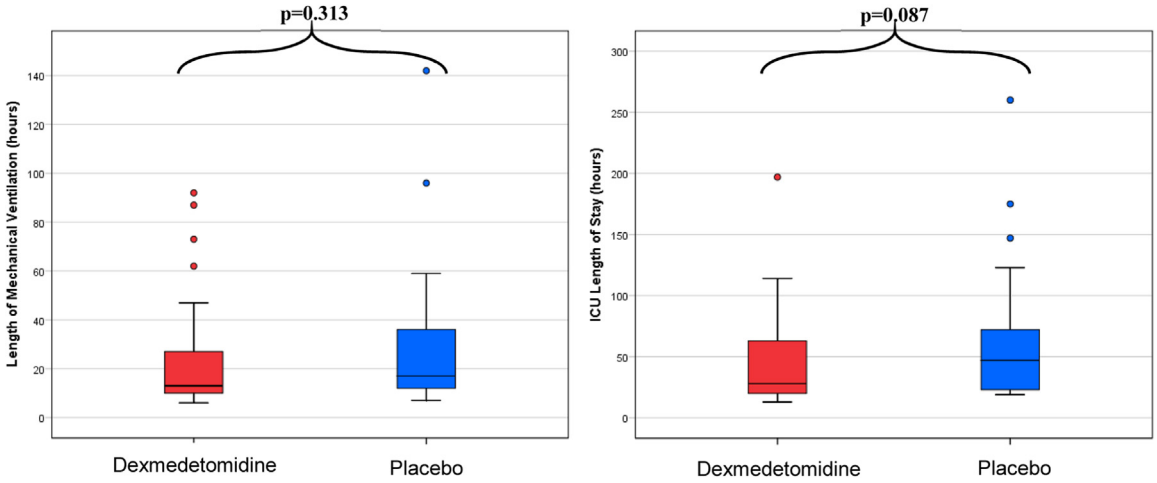


Fig 4. Comparison of duration of mechanical ventilation and intensive care unit length of stay between groups. The error bar represents 95% CI. *p < 0.05 (statistically significant).

manifestation of lower blood pressure, easing blood flow through the systemic circulation.[34] Deregulation of catecholamine by DEX also could have yielded lower vascular muscle tone.[35] All these results suggest that DEX was able to minimize postoperative cardiac dysfunction and protect against cardiac insults from CPB-related reperfusion injury. In this study, the highest VIS was significantly lower in the Dex group compared with that of the placebo group, implying adequately preserved peripheral perfusion.[36] This positive effect also was found when administering DEX during surgery to prevent the future occurrence of junctional ectopic tachycardia, which may deteriorate hemodynamic performance and affect the VIS. Using DEX's effect of slowing heart rate, it is one of the therapeutic options recommended for control of tachyarrhythmia incidence (eg, junctional ectopic tachycardia) after pediatric cardiac surgery.[37] However, the emergence of symptomatic bradycardia or high-grade atrioventricular block ought to be observed during postoperative monitoring, as DEX could produce these side effects.

The length of MV (13 *v* 17 hours, Dex *v* placebo, respectively; p = 0.313) and ICU LOS (28 *v* 47 hours, Dex *v* placebo, respectively; p = 0.087) was not distinct between groups. A study published in 2017 found that DEX did not significantly reduce the length of MV compared with a placebo. One possible explanation is that DEX's ability to maintain its sedative properties up to several hours after the last administration could have led to more time spent unawake, potentially contributing to a longer duration of MV in some patients.[38] This result positively correlates with a study randomizing 182 infants, showing no significant difference in the duration of MV between the Dex and the placebo group. Although DEX did not significantly reduce the length of MV, it also did not significantly reduce ICU LOS.[39] On the other hand, a contradictory finding was found in a meta-analysis of 8 randomized controlled trials, which showed that ICU LOS was significantly decreased in the group treated with DEX (mean difference −4.45 hours, 95% CI −8.52 to −0.38; p = 0.03). However, this result was associated with potential heterogeneity ($I^2$ = 79%).[40] Ultimately, the postoperative 30-day mortality exhibited no difference between groups. This finding was closely associated with zero deaths in both groups, which could manifest as statistically insignificant results.

The authors would like to highlight that this study involved cyanotic TOF as its main characteristic of the populations. Choosing this type of participant heightens insights into DEX's effectiveness in alleviating cardiac injuries when we come across modestly perfused ventricular muscles (commonly called capillary/myocytes mismatch) in TOF.[6] Furthermore, this study focused on the efficacy of DEX when given as a priming solution in the CPB machine, followed by intravenous infusion. For safety reasons, the method of DEX administration in this trial adhered to the one in a previously published study by Zhang et al., which compared the cardioprotective effect of DEX given as a priming solution versus intravenous infusion during bypass.[15] Only a few trials emphasized administering DEX perioperatively as infusion post-bypass, not yet providing sufficient evidence to be implemented safely in centers in Indonesia. Additionally, this trial did not administer DEX before bypass (eg, starting from skin incision), as it may increase the risk of spell due to its effect on reducing systemic vascular resistance.[34]

### *Limitations of the Study*

There are several limitations in this study. First, human factors accounted for patients' surgical intervention and postoperative management could not specifically be identified. They may render diverse degrees of inflammation and myocardial injuries. In addition, the median age of this study population was about 41 months old, which is not considered the ideal age for elective TOF repair. The older population in this trial may limit the study's applicability in other countries where TOF repair is indicated commonly for patients aged between 3 and 11 months. Finally, this trial showed that DEX has little effect in reducing mortality and morbidity in ICU despite exhibiting a cardioprotective effect proven by laboratory and echocardiographic exams. Thus, future trials with larger sample sizes may provide clarity toward those clinical outcomes.

## Conclusion

In the TOF children undergoing CPB, DEX reduced postoperative cardiac injuries through attenuation of troponin I release. In addition, DEX minimized inflammatory response and tissue hypoxia during and after CPB use, as shown by the significant decrease in both IL-6 and lactate production. Furthermore, several hemodynamic parameters, such as cardiac index, cardiac output, and systemic vascular resistance, were improved along with the VIS. No difference was found in terms of length of MV and ICU LOS, as well as 30-day mortality in both groups. We concluded that DEX-contained priming solution and infusion in the CPB machine is an effective cardioprotective agent in TOF children undergoing open heart surgery.

## Declaration of Competing Interest

None.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2023.10.004.

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