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High Dose Methylprednisolone versus Low Dose in Correction of Congenital Acyanotic Heart Disease

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ABSTRACT

Background: A large number of pediatric patients undergoing congenital heart disease corrective procedures receive peri-operative corticosteroids, aiming to reduce post-operative inflammation and capillary leak following cardiopulmonary bypass (CPB). This study aimed to compare the effect of different doses of methylprednisolone on inflammatory mediators' production and effect on myocardium.

Methods: A trial was conducted on pediatric patients undergoing surgical correction for congenital acyanotic lesion needing CPB machine. Patients were divided into 3 groups: group A patients received 10 mg/kg methylprednisolone (MP) after induction, group B received 30 mg/kg MP and group C patients received placebo.

Results: Serial measurement of serum troponin, IL6 and random blood sugar showed no differences in the 3 studied groups at the first measurement, and random blood glucose at ICU admission and hour-24 were highest in the high-dose group (IL6 was lowest) with P value <0.001. Troponin showed no difference at ICU admission, while at hour-24, it was lowest in the high-dose group with p value<0.001, followed by the low-dose group and the highest in control. The ejection fraction (EF) at hour-6 was highest in the high-dose group with p value<0.001, followed by the low-dose group and lowest in control. The vasoactive inotrope score was lowest in high-dose followed by low-dose groups followed by control. As regards complications, there was no different significance between groups.

Conclusion: High-dose MP (30 mg/kg) given to pediatric patients undergoing surgical correction of congenital acyanotic heart disease showed better outcomes such as less elevation of inflammatory mediators, lower level of troponin, vasoactive score and higher ejection fraction, with no additional complications recorded.

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Pediatrics; cardiac surgery; cardiopulmonary bypass; methylprednisolone; inflammatory mediators

1. Background

Many children undergoing correction for congenital heart disease receive peri-operative corticosteroids with the aim of reducing the release of post-operative inflammation and capillary leak following CPB. Using CPB is essential for most cardiac operations; however, it is known that it is responsible for systemic inflammatory response (SIR). SIR is caused by the contact of the blood with foreign surfaces and hypothermia. This is aggravated by ischemia reperfusion injury. This complex inflammatory reaction may be the cause of post-operative complications such as ventricular dysfunction and multiorgan failure [1]. CPB activates the complement system, which caused granulocyte activation and release of oxygen free radicals such as superoxide oxygen, hydrogen peroxide, hydroxyl radical and singlet oxygen; they all act mainly on membrane lipids to increase membrane permeability and worsen cardiac and pulmonary function [2]. In addition to free radical production, CPB stimulates systemic cytokine release. The release of cytokines during CPB has dangerous effects on heart and other systems such as liver, kidney and brain. Pro-inflammatory cytokines such as tumor necrosis factor TNF, interleukin 1(IL-1), interleukin 6(IL-6) and interleukin 8(IL-8) can affect the myocardial contractility and peripheral circulation and produce direct damaging effects on other organs [2]. Interleukin-6 (IL-6) is induced by (TNF)-α and reflects the localized TNF-α activity, suggesting the important role of TNF-α and IL-6 in the response after cardiac surgery. However, the relation between IL-6 and the adverse outcome after cardiac surgery has not been investigated yet [3]. Moreover, in congenital cardiac surgery, the modulation of SIR is important as it is believed that the inflammatory response is aggravated by the surface of the CPB circuit relative to the small circulating blood volume of young patients, the use of deep hypothermic circulatory arrest (DHCA) and more hemodilution [4].Corticosteroids have been used commonly in congenital heart surgical procedures for anti-inflammatory and cardioprotective purposes, it has been found that corticosteroids decreased post-operative cardiac troponin production and some studies found that corticosteroids have decreased the

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duration of postoperative mechanical ventilation and shortened the length of stay in intensive care [5]. MP is given in congenital cardiac surgery to protect against the relative adrenal insufficiency that can occur due to acute stress of surgery, and another benefit of corticosteroids in congenital cardiac surgery is the neuroprotective effect during DHCA [6].

The released cytokines TNF, IL-6 and IL-8 are released after normothermic CPB, and they mediate the occurrence of postoperative vasodilation. Corticosteroids may decrease the cytokine release after normothermic CPB and reduce postoperative vasodilation. This study prospectively searched for the release of IL-6 in patients undergoing CPB, both with pretreatment of different doses of MP.

2. Aim of this work

The aim of this work is to compare the result of the use of low-dose versus high-dose MP on inflammatory mediators' level and their myocardial protective effect after CPB in congenital acyanotic cardiac surgery.

3. Methodology

This study was approved by our institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. The trial has been registered with a clinical trial registry (NCT05103397). We obtained informed written consents from the parents of the participants, and we were responsible for maintaining the confidentiality of the data.

This prospective, blinded, parallel group (one: one allocation ratio), randomized, controlled clinical trial was conducted at the University Hospitals (Cardiovascular Surgery Hospital, Thoracic Surgery Unit), between 16 October 2021 and 15 January 2022. Randomization was performed using a computer-generated randomization sequence. The attending doctor who gave the drug was not involved in collecting the data and was replaced after giving the drugs. Both the investigator and the intensivist were blinded to the drug given.

4. Inclusion criteria

We included pediatric patients [1–16] years old undergoing surgical correction for congenital acyanotic cardiac lesion needing a cardiopulmonary bypass machine.

5. Exclusion criteri

Patients with the following conditions were excluded: cyanotic cardiac patients undergoing closed cardiac surgeries (off pump), previous cardiac surgery, history of neurological disease, diabetics, emergency procedures, patients on preoperative steroid therapy and adult patients with congenital heart disease.

Full laboratory tests were performed for all patients prior to the scheduled procedure. For all patients in this study, preoperative evaluation was performed, and airway examination tests (mouth opening, mallampati grading, thyromental distance and evaluation of dentition) were performed. Fasting hours according to standard guidelines was checked [7]. On patient's arrival to the operating theater, either induction of anesthesia by an inhalational technique using sevoflurane 4–6% followed by an intravenous (IV) line insertion or induction by ketamine 1–2 mg /kg and 0.01 mg/kg atropine was performed. The standard protocol of monitoring includes electrocardiography (ECG) and pulse oximetry (SpO2). Fentanyl 1–5 microgram/kg was given during preoxygenation with 100% oxygen, followed by non-depolarizing muscle relaxant (atracurium 0.5 mg/kg), and then endotracheal intubation was performed, confirmed by capnography [8]. Femoral artery cannulation (with or without the ultrasound-guided technique) by 20 G Leader catheter for the invasive blood pressure (BP) measurement was performed, and a triple lumen central line was inserted in internal jugular vein (BRAUN) by the ultrasound-guided technique. After finishing all anesthesia processes, a blood sample (2 ml) was taken to measure (IL6), troponin I and blood glucose level. Skin incision followed by median sternotomy was performed, and then Heparin 300–500 IU/kg was given to achieve an ACT of 450–480 before starting CPB before aortic cannulation and start connecting the CPB circuit. Patients were divided into 3 groups:

Group (A) patients received 10 mg/jg MP after induction of anesthesia (25 patients) [8].

Group (B) patients received 30 mg/kg MP after induction of anesthesia (25 patients) [5].

Group (C) **(control group)** patients received placebo in the form of normal saline after induction of anesthesia (25 patients).

After surgical repair of cardiac lesion and separation of CPB, support of the heart was achieved and maintained by milrinone 0.3–0.7 ug/kg/min together with noradrenaline 0.01–1 ug/kg/min if needed according to each patient data [9]. Reversal of heparin was performed by protamine sulphate 1:1 correction. BP and HR were recorded every 10 minutes. After finishing hemostasis and chest closure, patients were meticulously transferred to ICU.

The inotropic support for each patient was estimated according to the maximum vasoactive inotropic score (VIS). Maximum VIS for both the first 24 hrs and the next 24 hrs was calculated. It was calculated according to the study by Gaies et al. as follows: VIS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100

x epinephrine dose (mcg/kg/min) +10 x milrinone dose (mcg/kg/min) + 10,000 x vasopressin dose (U/kg/min) + 100 x norepinephrine dose (mcg/kg/min). Inotropes and vasopressors were added after CPB if the systolic blood pressure is less than 90 mmHg in adequately preloaded patients [9].

Then, when the patient was in the ICU, another blood sample (2 ml) to measure IL6, troponin and random blood sugar was taken, and a third sample was withdrawn after 24 hours. Vital data were monitored and recorded every 30 minutes until extubation. Time of extubation was also recorded. Complications like neurological events, incidence of new arrhythmia and wound infection were recorded.

6. Sample size

Using the G power program for sample size calculation, setting power at 80% and alpha error at 5% and reviewing results from previous studies [10] showed that a single low dose of methylprednisolone (10 mg/kg) reduces the inflammatory reaction during and after CPB, assuming the effect size difference (=0.4) between the different intervention groups regarding IL6 after CPB and after 10% adjustment for dropout rate and a sample size of 75 patients (divided into 3 groups, 25 patients per group).

7. Outcome

7.1. Primary outcome

The primary outcome is the level of IL 6 after CPB time

8. Secondary outcome

The secondary outcome is postoperative adverse effects related to high doses of steroid represented as the blood glucose level.

9. End of the study

The end point of the study was the change of surgical decision due to the presence of associated pathology that was not diagnosed before the planned surgery.

-Elevated random blood sugar level after induction.

The collected data were coded, tabulated and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data after being tested for normality using the Shapiro-Wilk test are described as mean ± SD (standard deviation) and then compared using the ANOVA test with the post hoc Bonferroni test. Qualitative data are described as number and percentage and compared using the Chi square test and Fisher's Exact test for variables with small, expected numbers. The level of significance taken at P values < 0.050 was significant; otherwise, it was non-significant.

9.1. Results

Ninety-three pediatric patients were scheduled for surgical correction of acyanotic heart disease. Only 75 patients met the eligibility to be included in this study (Figure 1). Surgical correction was performed by using CBP, and patients were differentiated according to different doses of methylprednisolone received after induction of anesthesia. Patients were divided into 3 groups:high-dose group received 30 mg/kg MP, low-dose group received 10 mg/kg MP and the control group did not receive MP. Both genders were included in the study with age ranging from 1–9 year (inclusion criterion was up to 16-year-old). There was no significant difference between 3 groups regarding demographic data, type of surgery, aortic cross clamp time represented in tables as part from CPB time recorded in 3 groups or time of extubation of patients postoperatively in ICU (Table 1). As regard intraoperative vital data, there was no statistical difference

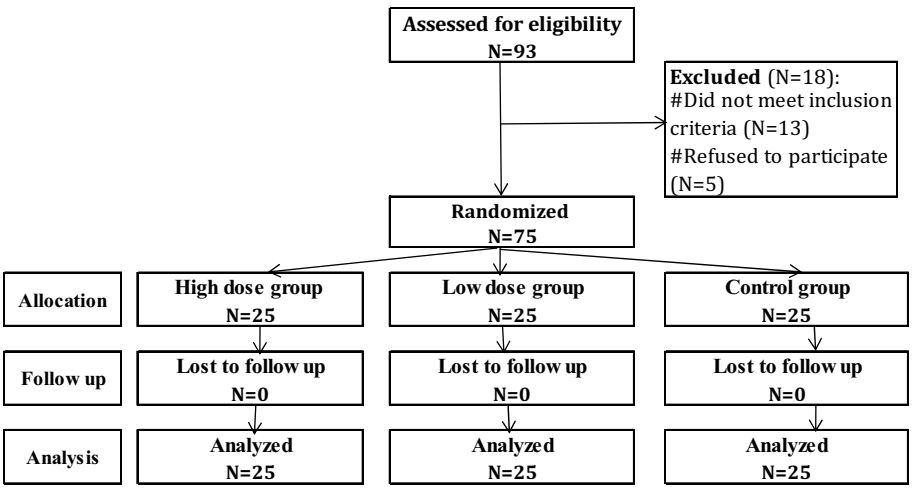

Figure 1. Flow diagram for the study.

Table 1. Demographic and operative characteristics among the studied groups.

Variables	High dose (n = 25)	Low dose (n = 25)	Control (n = 25)	p-value
Age (years)	5.2 ± 1.8	4.9 ± 2.1	5.6 ± 2.0	^0.443
Sex, (n, %)	11 (44.0%)	14 (56.0%)	13 (52.0%)	#0.688
• Male	14 (56.0%)	11 (44.0%)	12 (48.0%)	
• Female				
Weight (kg)	16.5 ± 3.7	15.9 ± 4.4	17.3 ± 4.1	^0.499
Types of Operation, (n, %)	11 (44.0%)	10 (40.0%)	12 (48.0%)	§0.733
• ASD	10 (40.0%)	8 (32.0%)	10 (40.0%)	
• VSD	4 (16.0%)	7 (28.0%)	3 (12.0%)	
• Partial A-V canal				
Intraoperative, Pre-bypass duration (minutes)	24.5 ± 3.1	23.5 ± 2.7	24.1 ± 2.7	^0.493
Intraoperative, Bypass duration (minutes)	48.6 ± 12.1	48.7 ± 12.1	45.9 ± 10.9	^0.636
Intraoperative, Post-bypass duration (minutes)	140.8 ± 12.4	145.3 ± 16.3	137.9 ± 16.9	^0.231
Total operative duration (minutes)	214.0 ± 20.4	217.5 ± 25.1	207.9 ± 26.0	^0.361
Postoperative ICU stay (hours)	10.3 ± 0.9	10.6 ± 0.8	10.4 ± 0.9	^0.468

Data presented as Mean ± SD unless mentioned otherwise. ^ANOVA test. #Chi square test. §Fisher's exact test.
No significant statistical differences between the studied groups regarding demographic and operative characteristics was observed

between the studied groups, and also, postoperative vital data showed the same finding (Tables 2 and 3). Serial measurements of serum troponin, IL6 and random blood sugar showed no differences in the 3 studied groups at the first measurement (after sternotomy), while the random blood glucose level at **ICU admission and hour-24** was highest observed in the high-dose group, followed by the low-dose group and lowest in the control group, and the differences statistically were significant between all of them. **IL-6 at ICU admission and hour-24** was lowest in the high-dose group, followed by the low-dose group and highest in the control group, and the differences statistically were significant between all of them. The **troponin level** showed no difference between 3 groups at the second measurements (at ICU admission), while **at hour-24**, it was lowest in the high-dose group, followed by the low-dose group and highest in the control group, and the differences were statistically significant only between the high-dose group and each of control and low-dose groups, with no significant difference between control and low dose groups (Table 4). Measuring outcomes in the form of **ejection fraction at hour-6** were highest in the high-dose group, followed by the low-dose group and lowest in the control group, and the differences were statistically significant only between the control group and each of high- and low-dose groups with no significant difference between high- and low-dose groups (Table 4). As regard intraoperative and postoperative complications, **heart block** did not occur in the high-dose group, but was recorded in the low-dose group (2 patients) and was most frequent in the control group (4 patients), but these differences did not show any statistical significance. The time, when post-bypass heart block occurred, was later in the low-dose

Table 2. Heart rate (beat/minute) among the studied groups.

					Effects of groups relative to each other			
Time	High dose (n = 25)	Low dose (n = 25)	Control (n = 25)	^p-value	Measures	High/Low	High/control	Low/control
Intraoperative, post-bypass								
Minute-0	109.3 ± 7.9	110.2 ± 8.7	107.3 ± 8.0	0.452	Mean ± SE	−0.9 ± 2.4	2.0 ± 2.3	2.9 ± 2.4
					95% CI	−5.6–3.9	−2.5–6.5	−1.9–7.6
Minute-30	109.3 ± 5.6	111.2 ± 8.4	107.4 ± 7.6	0.199	Mean ± SE	−1.9 ± 2.0	1.9 ± 1.9	3.8 ± 2.3
					95% CI	−5.9–2.2	−1.9–5.7	−0.8–8.3
Minute-60	109.0 ± 9.2	110.6 ± 10.4	106.4 ± 10.8	0.328	Mean ± SE	−1.6 ± 2.8	2.6 ± 2.8	4.3 ± 3.0
					95% CI	−7.2–3.9	−3.1–8.4	−1.7–10.3
Minute-90	109.7 ± 7.3	110.1 ± 9.8	106.4 ± 9.1	0.272	Mean ± SE	−0.4 ± 2.4	3.3 ± 2.3	3.7 ± 2.7
					95% CI	−5.3–4.5	−1.4–8.0	−1.7–9.0
End	111.1 ± 7.2	112.9 ± 8.6	108.7 ± 8.4	0.187	Mean ± SE	−1.8 ± 2.3	2.4 ± 2.2	4.2 ± 2.4
					95% CI	−6.4–2.7	−2.1–6.9	−0.6–9.1
Postoperative, ICU								
Hour-0	108.1 ± 7.9	110.1 ± 9.7	105.9 ± 9.3	0.270	Mean ± SE	−2.0 ± 2.5	2.2 ± 2.4	4.2 ± 2.7
					95% CI	−7.0–3.0	−2.7–7.1	−1.2–9.6
Hour-2	109.5 ± 7.9	109.8 ± 9.1	106.2 ± 8.8	0.274	Mean ± SE	−0.4 ± 2.4	3.2 ± 2.4	3.6 ± 2.5
					95% CI	−5.2–4.5	−1.5–8.0	−1.5–8.7
Hour-4	110.0 ± 8.2	111.6 ± 8.9	107.5 ± 9.0	0.254	Mean ± SE	−1.5 ± 2.4	2.6 ± 2.4	4.1 ± 2.5
					95% CI	−6.4–3.4	−2.3–7.5	−1.0–9.2
Hour-6	109.7 ± 7.4	110.5 ± 9.5	106.8 ± 8.4	0.274	Mean ± SE	−0.8 ± 2.4	2.9 ± 2.2	3.7 ± 2.5
					95% CI	−5.7–4.0	−1.6–7.4	−1.4–8.8
Hour-8	108.6 ± 8.1	110.1 ± 8.2	106.4 ± 8.9	0.293	Mean ± SE	−1.5 ± 2.3	2.2 ± 2.4	3.7 ± 2.4
					95% CI	−6.1–3.1	−2.6–7.1	−1.1–8.6
End	110.4 ± 9.5	111.9 ± 11.0	107.4 ± 11.8	0.327	Mean ± SE	−1.5 ± 2.9	3.0 ± 3.0	4.5 ± 3.2
					95% CI	−7.3–4.4	−3.0–9.1	−2.0–11.0

Data presented as Mean ± SD. ^ANOVA test. CI: Confidence interval. SE: Standard error
No significant statistical differences between the studied groups regarding heart rate.

Table 3. Mean blood pressure (mmHg) among the studied groups.

					Effects of groups relative to each other			
Time	High dose (n = 25)	Low dose (n = 25)	Control (n = 25)	^p-value	Measures	High/Low	High/Control	Low/Control
Intraoperative, post-bypass								
Minute-0	60.8 ± 3.2	60.4 ± 4.5	61.9 ± 4.0	0.409	Mean ± SE	0.4 ± 1.1	−1.0 ± 1.0	−1.4 ± 1.2
					95% CI	−1.8–2.6	−3.1–1.0	−3.8–1.0
Minute-30	61.3 ± 3.9	60.5 ± 5.4	61.9 ± 4.5	0.549	Mean ± SE	0.8 ± 1.3	−0.6 ± 1.2	−1.4 ± 1.4
					95% CI	−1.9–3.5	−3.0–1.8	−4.3–1.4
Minute-60	60.7 ± 3.3	60.3 ± 4.2	61.6 ± 3.8	0.433	Mean ± SE	0.4 ± 1.1	−1.0 ± 1.0	−1.4 ± 1.1
					95% CI	−1.7–2.5	−3.0–1.1	−3.7–0.9
Minute-90	61.6 ± 3.5	60.9 ± 3.9	62.7 ± 3.9	0.244	Mean ± SE	0.7 ± 1.1	−1.1 ± 1.0	−1.8 ± 1.1
					95% CI	−1.4–2.8	−3.2–1.0	−4.0–0.4
End	60.6 ± 3.5	60.0 ± 4.3	61.8 ± 3.8	0.250	Mean ± SE	0.6 ± 1.1	−1.2 ± 1.0	−1.8 ± 1.2
					95% CI	−1.7–2.8	−3.3–0.8	−4.1–0.5
Postoperative, ICU								
Hour-0	61.1 ± 3.3	60.9 ± 4.1	62.2 ± 3.9	0.443	Mean ± SE	0.2 ± 1.1	−1.1 ± 1.0	−1.3 ± 1.1
					95% CI	−1.9–2.3	−3.1–1.0	−3.6–1.0
Hour-2	61.1 ± 3.4	60.4 ± 4.5	61.9 ± 3.9	0.400	Mean ± SE	0.7 ± 1.1	−0.8 ± 1.0	−1.5 ± 1.2
					95% CI	−1.6–3.0	−2.9–1.2	−3.9–0.9
Hour-4	60.7 ± 3.6	60.6 ± 4.3	61.6 ± 3.8	0.616	Mean ± SE	0.0 ± 1.1	−0.9 ± 1.0	−1.0 ± 1.1
					95% CI	−2.2–2.3	−3.0–1.2	−3.3–1.3
Hour-6	61.3 ± 3.4	60.7 ± 4.5	62.8 ± 3.9	0.174	Mean ± SE	0.6 ± 1.1	−1.5 ± 1.0	−2.1 ± 1.2
					95% CI	−1.7–2.9	−3.6–0.6	−4.5–0.3
Hour-8	60.8 ± 3.7	60.0 ± 4.5	61.5 ± 4.2	0.457	Mean ± SE	0.8 ± 1.2	−0.7 ± 1.1	−1.5 ± 1.2
					95% CI	−1.6–3.2	−2.9–1.6	−4.0–1.0
End	60.1 ± 3.7	59.8 ± 4.1	61.1 ± 4.4	0.504	Mean ± SE	0.3 ± 1.1	−1.0 ± 1.1	−1.3 ± 1.2
					95% CI	−1.9–2.5	−3.3–1.3	−3.7–1.1

Data presented as Mean ± SD . ^ANOVA test. CI: Confidence interval. SE: Standard error
No significant statistical differences between the studied groups regarding mean blood pressure were observed.

group in comparison to the control group. It also lasted for a shorter duration with return of normal sinus rhythm in (1 patient) 50% of patients in the low-dose group, while only 25% of patients (1 patient) were recurred in the control group, yet the differences did not prove to be statistically significant. **Neurological**

Table 4. Ejection fraction, random blood glucose and IL-6 among the studied groups.

					Effects of groups relative to each other			
Time	High dose (n = 25)	Low dose (n = 25)	Control (n = 25)	^p-value	Measures	High/Low	High/Control	Low/Control
Ejection fraction (%)								
Hour-6	64.1 ± 2.7a	62.6 ± 3.2a	59.3 ± 3.2b	<0.001*	Mean ± SE	1.5 ± 0.8	4.8 ± 0.8	3.2 ± 0.9
					95% CI	−0.2–3.2	3.1–6.4	1.4–5.0
Random blood glucose (mg/dL)								
Sternotomy	89.8 ± 4.9	91.4 ± 4.6	91.1 ± 5.0	0.441	Mean ± SE	−1.7 ± 1.4	−1.3 ± 1.4	0.4 ± 1.4
					95% CI	−4.4–1.0	−4.1–1.5	−2.4–3.1
ICU admission	265.8 ± 28.2a	219.1 ± 21.0b	179.8 ± 17.2c	<0.001*	Mean ± SE	46.7 ± 7.0	86.0 ± 6.6	39.2 ± 5.4
					95% CI	32.6–60.9	72.7–99.2	28.3–50.2
Hour-24	269.0 ± 28.9a	222.5 ± 21.4b	181.3 ± 17.2c	<0.001*	Mean ± SE	46.6 ± 7.2	87.8 ± 6.7	41.2 ± 5.5
					95% CI	32.1–61.0	74.3–101.3	30.2–52.2
IL-6 (pg/mL)								
Sternotomy	113.8 ± 5.0	110.9 ± 5.9	112.6 ± 5.4	0.169	Mean ± SE	2.9 ± 1.5	1.3 ± 1.5	−1.6 ± 1.6
					95% CI	−0.2–6.1	−1.7–4.3	−4.9–1.6
ICU admission	221.3 ± 33.0a	260.2 ± 52.8b	311.4 ± 35.6c	<0.001*	Mean ± SE	−38.9 ± 12.5	−90.1 ± 9.7	−51.2 ± 12.7
					95% CI	−63.9–-13.8	−109.6–-70.5	−76.8–-25.6
Hour-24	107.7 ± 16.8a	124.5 ± 29.8b	154.0 ± 23.7c	<0.001*	Mean ± SE	−16.8 ± 6.8	−46.3 ± 5.8	−29.5 ± 7.6
					95% CI	−30.5–-3.1	−58.0–-34.6	−44.8–-14.2
Troponin (ng/mL)								
Sternotomy	0.008 ± 0.003	0.009 ± 0.003	0.008 ± 0.004	0.881	Mean ± SE	0.000 ± 0.001	0.000 ± 0.001	0.000 ± 0.001
					95% CI	−0.002–0.001	−0.002–0.002	−0.001–0.002
ICU admission	5.6 ± 1.4	5.8 ± 1.4	5.7 ± 1.9	0.885	Mean ± SE	−0.2 ± 0.4	−0.1 ± 0.5	0.1 ± 0.5
					95% CI	−1.0–0.6	−1.1–0.8	−0.8–1.1
Hour-24	1.9 ± 0.5a	2.8 ± 0.7b	3.3 ± 1.2b	<0.001*	Mean ± SE	−0.9 ± 0.2	−1.4 ± 0.3	−0.5 ± 0.3
					95% CI	−1.3–-0.6	−1.9–-0.9	−1.1–0.1
Inotrope support, (n, %)								
ICU admission	19 (76.0%)	21 (84.0%)	22 (88.0%)	§0.645	RR (95% CI)	0.91 (0.69 − 1.20)	0.86 (0.66 − 1.12)	0.96 (0.76 − 1.19)
Vasoactive score								
	(n = 19)	(n = 21)	(n = 22)					
ICU admission	4.7 ± 1.5a	8.2 ± 1.7b	9.2 ± 1.5b	<0.001*	Mean ± SE	−3.5 ± 0.5	−4.5 ± 0.5	−1.0 ± 0.5
					95% CI	−4.5–-2.5	−5.5–-3.6	−2.1–0.0
Hour-24	4.5 ± 1.4a	7.9 ± 1.7b	9.0 ± 1.4b	<0.001*	Mean ± SE	−3.4 ± 0.5	−4.5 ± 0.4	−1.0 ± 0.5
					95% CI	−4.4–-2.4	−5.4–-3.6	−2.0–-0.1

Data presented as Mean ± SD unless mentioned otherwise. §Fisher's exact test. ^ANOVA test with the post hoc Bonferroni test, homogenous groups had the same symbol "a, b, c". RR: Relative rate. CI: Confidence interval. SE: Standard error.

Table 5. Adverse effects among the studied groups.

Variables	High dose (n = 25)	Low dose (n = 25)	Control (n = 25)	§p-value	Effects of groups relative to each other			
					Measures	High/Low	High/control	Low/control
Neurological	1 (4.0%)	0 (0.0%)	1 (4.0%)	0.999	RR (95% CI)	NA	1.00 (0.07 − 15.12)	NA
Wound infection (superficial)	5 (20.0%)	3 (12.0%)	2 (8.0%)	0.584	RR (95% CI)	1.67 (0.45 − 6.24)	2.5 (0.53 − 11.7)	1.50 (0.27 − 8.22)
Heart block	0 (0.0%)	2 (8.0%)	4 (16.0%)	0.155	RR (95% CI)	NA	NA	0.50 (0.10 − 2.49)
		2	4					
Block beginning • Minute 0–30 • Minute 31–60	NA	1 (50.0%) 1 (50.0%)	3 (75.0%) 1 (25.0%)	0.999	RR (95% CI)	NA	NA	0.67 (0.15 − 2.98)
Block duration • ICU • Post-ICU	NA	1 (50.0%) 1 (50.0%)	1 (25.0%) 3 (75.0%)	0.999	RR (95% CI)	NA	NA	2.00 (0.22 − 17.89)

Data presented as (n, %). §Fisher's exact test. RR: Relative rate. CI: Confidence interval.

adverse effects were recorded only in high-dose (1 patient) and control groups (1 patient), in form fits, with no statistically significant differences between the studied groups. **Wound infection** was most frequent in the high-dose group (5 patients), followed by the low-dose group (3 patients) and least frequent in the control group (2 patients), yet the differences were statistically non-significant (Table 5).

10. Discussion

In this study, 93 patients suffering from congenital acyanotic heart disease, planned for surgical correction, were divided into 3 groups according to the dose of MP received just after induction. They either received a high dose of 30 mg/kg or a low dose of 10 m/kg, and the third group did not receive steroids at all. In our institution, IL 6 is the only available inflammatory marker to be measured. Only 75 patients completed the study; there were significant differences as regard the postoperative ejection fraction measured 6 hours after surgery. The two groups that received MP had a higher EF in comparison to the control group, with no significance between the high-dose group and the low-dose group. Random blood sugar showed highest elevation in the high-dose group at ICU admission and after 24 hours. No differences between groups as regard the rate of wound infection was observed. As regard IL6 measured at ICU and after 24 hours, values were lowest in the high-dose group and higher in the low-dose group, with significant differences between all three groups. Cardiac troponin showed a significant variation only after 24 hours, expressed by the lowest level in the high-dose group, followed by the low-dose group, and the highest troponin level in the control group. These differences were significant only between the high-dose group and the two other groups, and no significance between the low-dose group and the control group was observed.

CPB, although is used for surgical correction of congenital heart disease, surely causes much insult to the myocardium. Many drugs and/or surgical techniques were tried to minimize this insult. MP has been widely administered in pediatric and adult cardiac surgical correction due to its anti-inflammatory and cardioprotective properties although the benefits of steroid treatment have not been conclusive yet. Although there are many studies performed to evaluate the advantages of MP in pump cardiac surgery, there are still no proved data about the optimal dose of steroid that can be given to achieve the maximum desired effect with the least drawback [11]. In a study performed in 2021, EuroScore and IL-6 in cardiac surgery were used. They found that a higher EuroScore (calculated before operation) and high IL-6 levels (6 hr after operation) had a prolonged mechanical ventilation and a longer ICU stay with an increase in mortality [12]. Although the development of CPB techniques, it still leads to activation of the coagulation, fibrinolytic, and inflammatory system. These changes are caused by the exposure to the artificial surface of the circuit. The consequences are degranulation of leukocytes and release of cytotoxic and inflammatory mediators as interleukins. IL6 is secreted by lymphocytes, fibroblasts, macrophages and endothelial cells. IL-6 itself is considered the important proinflammatory mediator found in the inflammatory processes. It is also suggested that IL6 is produced by the myocardium during the time of compromised myocardial function because of ischemia and reperfusion events. Surgical trauma might also increase the level of IL-6 within the first 4 to 6 h after surgery [13].

In a randomized double-blinded study performed on 30 children 1–18 months old scheduled for total TOF repair, different doses of MP were given at induction of anesthesia 30 mg/kg versus 5 mg/kg. There was no variation in interleukin (IL)-6, –8 or–10 concentrations, or leukocyte count. Also, it was found that there were no significant differences in TnT concentrations, SvO2, lactate concentrations, inotropic scores or levels of NT-pro BNP, suggesting no beneficial effects of dose on the myocardial protection [14]. In another study performed on 30 children with a mean age of 4 years operated to repair various congenital heart defects with CPB, comparing the effect of MP 30 mg/kg with that of MP 2 mg/kg before the onset of CPB performed 15 years earlier, the results showed comparable levels of IL-6 and –8 concentrations, C-reactive protein and neutrophils between the 2 groups. There were also no differences in outcome parameters such as oxygenation, duration of mechanical ventilation and Length of ICU stay [15].

A study was performed on neonates undergoing cardiac surgery with CPB, and patients either received 30 mg/kg MP or 10 mg/kg aimed to measure IL6 and IL10. The results showed no differences in the area under the curve for IL-10. As for IL-6, the area under the curve was significantly, but minimally lower for the 30 mg/kg dose ($p < 0.01$) and also, the area under the curve of IL6 concentration showed the same results when an added preoperative dose was given ($p < 0.01$) [16]. Different studies were performed and showed that MP was complicated with a hyperglycemia, which needed treatment with insulin. This effect occurred with doses ranging from 30 to 2 mg/kg. A study tested the different doses giving MP 30 vs. 5 mg/kg, and a significant difference in glucose levels was found, with higher glucose levels 6 h after CPB and the first postoperative day in the group receiving MP 30 mg/kg. It cannot be concluded that lower MP doses lead to a lower blood glucose level, as it was found that similar glucose concentrations have been recorded after an MP dose of 30 mg/kg and a dose of 2 mg/kg by the same

researchers [17]. The significance of the effect of the high glucose level in pediatric cardiac surgery is still not conclusive. In a prospective cohort study of 379 children with a mean age of 52 months (range 0.2–180 months), undergoing repair or palliation of a congenital heart defect and receiving MP 30 mg/kg showed an incidence of hyperglycemia (glucose concentration >7 mmol/l) of 86%. Severe hyperglycemia, defined as glucose concentrations >11.1 mmol/l, was associated with an increased in mortality and a higher infection rate in a multivariate analysis. In a retrospective study of 144 neonates with a body weight <10 kg undergoing cardiac surgery with CPB, no complications due to hyperglycemia took place. In a multicenter randomized controlled trial performed on 980 patients aged 0–36 months undergoing pediatric cardiac surgery with CPB, comparing tight glycemic control with standard care in the ICU, there was no better outcome of tight glycemic control on the incidence of infection, mortality, length of ICU stays or in the hospital and organ-specific complications [18].

The peak effect of intravenous MP occurs around 1 to 4 hours after administration, so a study was performed comparing the intraoperative MP alone with the combined preoperative and intraoperative MP administration. They found that the 2 doses have shown reduced myocardial and lower levels of systemic inflammatory mediators. In addition, treatment with steroid stimulated synthesis of the anti-inflammatory cytokine IL-10. Attenuation of inflammatory mediator expression was associated with increased O_2 delivery, decreased fluid requirements, lower body temperature and better trend in clinical outcomes. Compared with intraoperative steroid administration, combined pre- and intraoperative steroid treatment ameliorated systemic and myocardial inflammatory mediator release more effectively and was associated with improved indices of O_2 delivery in the first 24 hours after congenital cardiac surgery. These findings need to be confirmed by running large multicenter trial [19]. Using steroids will continue to be a matter of debate, many large multicenter, randomized controlled trials should be performed to be able to detect any treatment effect in congenital cardiac surgery that is operated nowadays with recording and comparing morbidity and mortality. These trials need to be similar in design to the large steroid trials performed in adult cardiac surgery [11]. A randomized controlled study was performed to test and detect the two most common timing of corticosteroid administration in children undergoing cardiac surgical procedures (ie, a single dose of MP given after the induction and administration in the CPB prime circuit). MP was either given at induction or in the CPB prime in children undergoing surgical correction of VSD or AVSD. Similar MP plasma concentrations were attained, and only the peak concentrations in the induction group occurred earlier. Administration at induction showed lower plasma concentrations of proinflammatory cytokine IL-8 immediately after weaning from CPB and 6 hours after CPB compared with both placebo and CPB prime. Troponin levels in both MP groups were significantly lower 6 hours after weaning from CPB compared with placebo. The study showed that early administration of steroids has anti-inflammatory properties and cardioprotective effects. However, the actual clinical data of these findings for this type of cardiac surgical procedure with a relatively short duration of CPB could not be shown [20].

In our study, we were able to show the beneficial effect of giving high dose of MP to pediatric patients with congenital acyanotic heart disease undergoing surgical correction using CBP. The study showed not only better outcomes as regard less elevation of inflammatory mediators and less vasoactive score recorded but also no more complications. Patients were followed up in the early postoperative period, with no collected data in the later stage to record any additional side effects or new occurrence of complications, plus the resultant data were obtained from a small sample size that cannot give the privilege to recommend the addition of MP, nor less than specific dose.

11. Conclusion

High-dose MP (30 mg/kg) given to pediatric patients undergoing surgery for congenital acyanotic heart disease showed better outcomes as regard less elevation of inflammatory mediators, lower level of troponin, lower vasoactive score and higher ejection fraction, with no additional complications recorded due to the higher glucose level.

Disclosure statement

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