Assessment of the Effect of Two Regimens of Milrinone Infusion in Pediatric Patients Undergoing Fontan Procedure: A Randomized Study

Abstract

Objective: The aim of the study was to compare the effect of two different regimens of milrinone on hemodynamics and oxygen saturation in pediatric patients undergoing Fontan procedure. **Design:** This was a randomized study. **Setting:** Cardiac centers. **Patients:** This study included 116 patients undergoing Fontan procedure. **Material and Methods:** Group E: Milrinone was started as infusion 0.5 µg/kg/min without a loading dose at the beginning of cardiopulmonary bypass (CPB) followed by infusion 0.5–0.75 µg/kg/min in the pediatric cardiac surgical intensive care unit (PSICU). Group L: Milrinone was started as a loading dose 50 µg/kg over 10 min before weaning from CPB followed by infusion 0.5–0.75 µg/kg/min in the PSICU. **Measurements:** Heart rate, mean arterial blood pressure, central venous pressure, transpulmonary pressure, cardiac index, pharmacological support, lactate level, urine output, oxygen saturation, ICU, and hospital length of stay. **Main Results:** There were no changes in the heart rate and mean arterial blood pressure ($P > 0.05$). The increase in the postoperative central venous pressure, transpulmonary pressure and lactate level was lower in Group E than Group L ($P < 0.05$). The increase in the postoperative cardiac index, oxygen saturation, and urine output was higher in Group E than Group L ($P < 0.05$). The requirement for pharmacological support was lower in the Group E ($P < 0.05$). The ICU and hospital length of stay were shorter in the Group E than Group L ($P < 0.05$). **Conclusion:** Early use of milrinone during Fontan procedure facilitated the weaning from CPB, decreased the elevation in the central venous pressure, transpulmonary gradient pressure, and the requirement for pharmacological support. Furthermore, it increased the cardiac index and arterial oxygen saturation.

Keywords: *Fontan procedure, hemodynamics, milrinone, oxygen saturation, pediatric patients*

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Introduction

The Fontan procedure is used mainly for patients with complex cardiac malformations a single functional ventricle such as tricuspid atresia, pulmonary atresia with intact ventricular septum, double inlet ventricle, hypoplastic left heart syndrome, or hypoplastic right heart syndrome.[1,2] Through Fontan operation, the whole systemic venous return is directed to the pulmonary arteries; and therefore, there is no pulmonary ventricle, so the pulmonary blood flow and preload to the systemic ventricle are critically dependent on the transpulmonary pressure gradient. Systemic vasodilatation is required after the Fontan operation, to reduce afterload on the systemic ventricle and to maintain a low pulmonary vascular resistance to augment the pulmonary blood flow.[3-5]

Milrinone is a Type III phosphodiesterase inhibitor and it is used as an effective medication for the patients with preexisting pulmonary hypertension or depressed postoperative cardiac function as it has inotropic, vasodilatory, and lusitropic effects. Therefore, it produces relaxation of the vascular smooth muscle and improves both systolic and diastolic cardiac function. Its usage has become a first-line choice for patients with various extents of pulmonary hypertension.[6-8] Milrinone is a drug commonly used to support cardiac output after congenital heart surgery in neonates, infants, and children.[6] In pediatric patients undergoing the Fontan procedure, milrinone is often used in the perioperative period in many centers.[3]

The aim of present study was to compare the effect of two different regimens of milrinone administration on hemodynamics and oxygen saturation in pediatric patients undergoing Fontan procedure.

Material and Methods

After obtaining informed consent and approval of local ethics and research

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committee in two cardiac centers, a double-blind randomized study included 116 pediatric patients (age 4.6–5.8 years) undergoing Fontan procedure. The inclusion criteria included primary Fontan procedure (not redo or revision Fontan procedure), patients with tricuspid atresia, pulmonary atresia with intact ventricular septum, double inlet ventricle, hypoplastic left heart syndrome, hypoplastic right heart syndrome, and the American Society of Anesthesiologists physical status classification system Score III or IV. Exclusion criteria included patients with preoperative pulmonary hypertension, revision surgery for failing Fontan procedure, preoperative low cardiac output syndrome, preexisting renal failure, preexisting thrombocytopenia, preoperative use of milrinone or known allergy to study medication. The concealment of allocation was done using random numbers generated through excel into two equal groups ($n = 58$ each). The study medication was prepared in 50 ml syringe in the main pharmacy and given to the anesthetist.

Anesthetic technique

The patients received Phenergan orally 0.5 mg/kg 2 h before surgery in the wards. Before induction of anesthesia noninvasive monitors (electrocardiography, pulse oximeter, and noninvasive blood pressure) were fixed. Induction of anesthesia was done for all patients by administration of intravenous ketamine (1–2 mg/kg) or thiopentone (3–5 mg/kg) followed by fentanyl (1–2 µg/kg) and pancuronium (0.1 mg/kg). After tracheal intubation, anesthesia was maintained with oxygen (100%), and sevoflurane (1%–3%) in addition to bolus dose of fentanyl (1–2 µg/kg) or morphine (0.1 mg/kg). The end-tidal $PaCO_2$ was maintained between 30 and 35 mmHg. After induction, invasive monitoring such as arterial line and central venous line were inserted. The cardiopulmonary bypass (CPB) circuit was primed with an average of 250 ml of a combination of plasmalyte, 20% albumin, and whole blood to achieve a hematocrit around 30%. All procedures were done under CPB and with aortic cross-clamping. Before weaning from CPB, the catheter was inserted into left atrium through the right superior pulmonary vein. Furosemide was given as a bolus dose of 5–10 mg in case of need to increase urine output. The patients were classified randomly into two groups:

- Group E: (early milrinone group) Milrinone was started as infusion 0.5 µg/kg/min without a loading dose at the beginning of CPB and continued postoperatively (0.5–0.75 µg/kg/min) in the pediatric cardiac surgical intensive care unit (PSICU)
- Group L: (late milrinone group) Milrinone was started as a loading dose 50 µg/kg over 10 min before weaning from CPB and continued as infusion (0.5–0.75 µg/kg/min) postoperatively in the PSICU.

During and after weaning from CPB, the oxygen concentration was 50%–100%. After surgery, all patients were transferred to the PSICU and maintained ventilated mechanically on oxygen: Air 50% and positive end-expiratory pressure (PEEP) 0–3 cm H_2O if needed. In ICU, all patients received furosemide (2 mg/kg/day) and spironolactone (2 mg/kg/day) [these diuretics were given through 3 doses in the nasogastric tube].

Patient monitoring

For all patients, the following variables were closely monitored; the heart rate, mean arterial pressure, central venous pressure, transpulmonary pressure gradient (difference between central venous pressure and left atrial pressure), cardiac index, pharmacological support (dopamine, epinephrine), pacing, lactate level, urine output, and arterial blood gases. Cardiac index was measured by two-dimensional echocardiography using modified Simpson's rule to calculate the cardiac output (Stroke volume and heart rate) and dividing the cardiac output over the body surface area. The readings were recorded at the following time points; T1: 15 min after weaning from CPB; T2: At the end of surgery; T3: 6 h after ICU admission; T4: 12 h after ICU admission; T5: 24 h after ICU admission; T6: 36 h after ICU admission; T7: 48 h after ICU admission.

Outcomes

The primary outcome was the postoperative hemodynamic stability assessed by heart rate, arterial blood pressure, central venous pressure, transpulmonary pressure gradient, urine output, and the improvement of the postoperative arterial oxygen saturation. The secondary outcome was the safety of the study medications, which was assessed by the occurrence of any adverse events.

Sample size calculation

Power analysis was performed using the Chi-square test for independent samples on the frequency of hemodynamic instability and desaturation postoperatively because it was the main outcome variable in the present study. A pilot study was done before starting this study because there are no available data in the literature for the comparison and effect of two regimens of milrinone infusion on hemodynamic instability and desaturation in pediatric patients undergoing Fontan procedure. The results of the pilot study (eight patients in each group) showed that the incidence of hemodynamic instability and desaturation was 25% in early milrinone infusion group, and 50% in late milrinone infusion group. Taking power 0.8, alpha error 0.05, and beta 0.2, a minimum sample size of 58 patients was calculated for each group.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the

Student's *t*-test for independent samples. Within group comparison of numerical variables was done using paired *t*-test. For comparing categorical data, Chi-square test was performed. The exact test was used instead when the expected frequency is <5. The $P < 0.05$ was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

All included patients completed the study. There were no significant differences regarding the demographic data, surgical history, type of congenital cardiac lesions, and data of preoperative catheterization and medications ($P > 0.05$) [Table 1].

Figure 1 shows the changes in the hemodynamics in the patients of the two groups. There was no difference in the hemodynamics before surgery according to the preoperative data of cardiac catheterization. The heart rate increased in the patients of the two groups, but the difference between the two groups was insignificant ($P > 0.05$) [Figure 1a]. The changes were minimal in the mean arterial blood pressure between the two groups ($P > 0.05$) [Figure 1b]. The central

venous pressure increased in the patients of the two groups after weaning from CPB, but the increase was lower in Group E than Group L ($P < 0.05$) [Figure 1c]. The left atrial pressure increased after weaning from CPB in the patients of the two groups, but the increase was lower in Group E than Group L ($P < 0.05$) [Figure 1d]. The transpulmonary gradient pressure was lower in patients of Group E than Group L after CPB ($P < 0.05$) [Figure 1e]. The cardiac index increased in the patients of the two groups after weaning from CPB, but the increase was higher in Group E than Group L ($P < 0.05$) [Figure 1f]. The arterial oxygen saturation increased after weaning from CPB in the patients of Group E than Group L ($P < 0.05$) [Figure 1g]. The serum lactate level increased after weaning from CPB in the patients of the two groups, but the increase was lower in Group E than Group L ($P < 0.05$), and the lactate level decreased after the first postoperative 24 h to be around the preoperative level [Figure 1h].

Table 2 shows the intraoperative data and outcomes of patients of the two groups. There was no difference in the surgical technique, CPB time, aortic cross-clamping time, thorax closure time, postoperative temporary pacemaker, transfused blood products, hemoglobin, or complications. The total milrinone dose was significantly higher in

Table 1: Preoperative data of patients			
Variable	Group E (*n*=58)	Group L (*n*=58)	*P*
Age (year)	5.21±1.80	5.30±1.75	0.785
Gender (male:female)	25:33	31:27	0.352
Weight (kg)	16.45±5.36	17.25±6.51	0.471
Body surface area (m^2)	0.56±0.24	0.54±0.21	0.633
Hemoglobin (g/dL)	16.37±5.30	15.85±5.14	0.592
Preoperative pacemaker	18	15	0.540
Preoperative diagnosis			
Tricuspid atresia	25	22	0.705
Pulmonary atresia with intact septum	15	19	0.541
Hypoplastic left ventricle syndrome	5	3	0.716
Double-outlet right ventricle	8	10	0.798
Left ventricular double outflow tract	5	4	0.728
Prior staging with Glenn procedure	48	45	0.642
Ejection fraction (%)	66.82±5.13	68.04±4.20	0.163
Pre-Fontan catheterization			
Preoperative systemic oxygen saturation (%) (T0)	81.53±4.72	82.19±4.25	0.430
Preoperative mPAP (mmHg)	15.22±2.16	14.89±1.95	0.389
Right atrial pressure (CVP) (mmHg) (T0)	12.82±2.64	11.55±2.32	0.116
Left atrial pressure (mmHg) (T0)	8.86±2.75	9.15±2.59	0.559
Transpulmonary gradient (mmHg) (T0)	6.10±2.24	5.86±2.75	0.607
Cardiac index (L/min/m^2) (T0)	2.35±1.63	2.50±1.68	0.626
Heart rate (bpm) (T0)	118.55±13.48	117.26±12.90	0.599
Mean arterial blood pressure (mmHg) (T0)	61.35±10.43	62.13±11.27	0.699
Serum lactate level (mmol/L) (T0)	1.62±0.74	1.54±0.72	0.556
Furosemide	58	58	1.000
Aspirin	48	45	0.642

Data are presented as mean±SD, *n*, %. Group E: Early milrinone group, Group L: Late milrinone group, mPAP: Mean pulmonary arterial pressure, CVP: Central venous pressure, T0: Preoperative readings, SD: Standard deviation, *n*: number
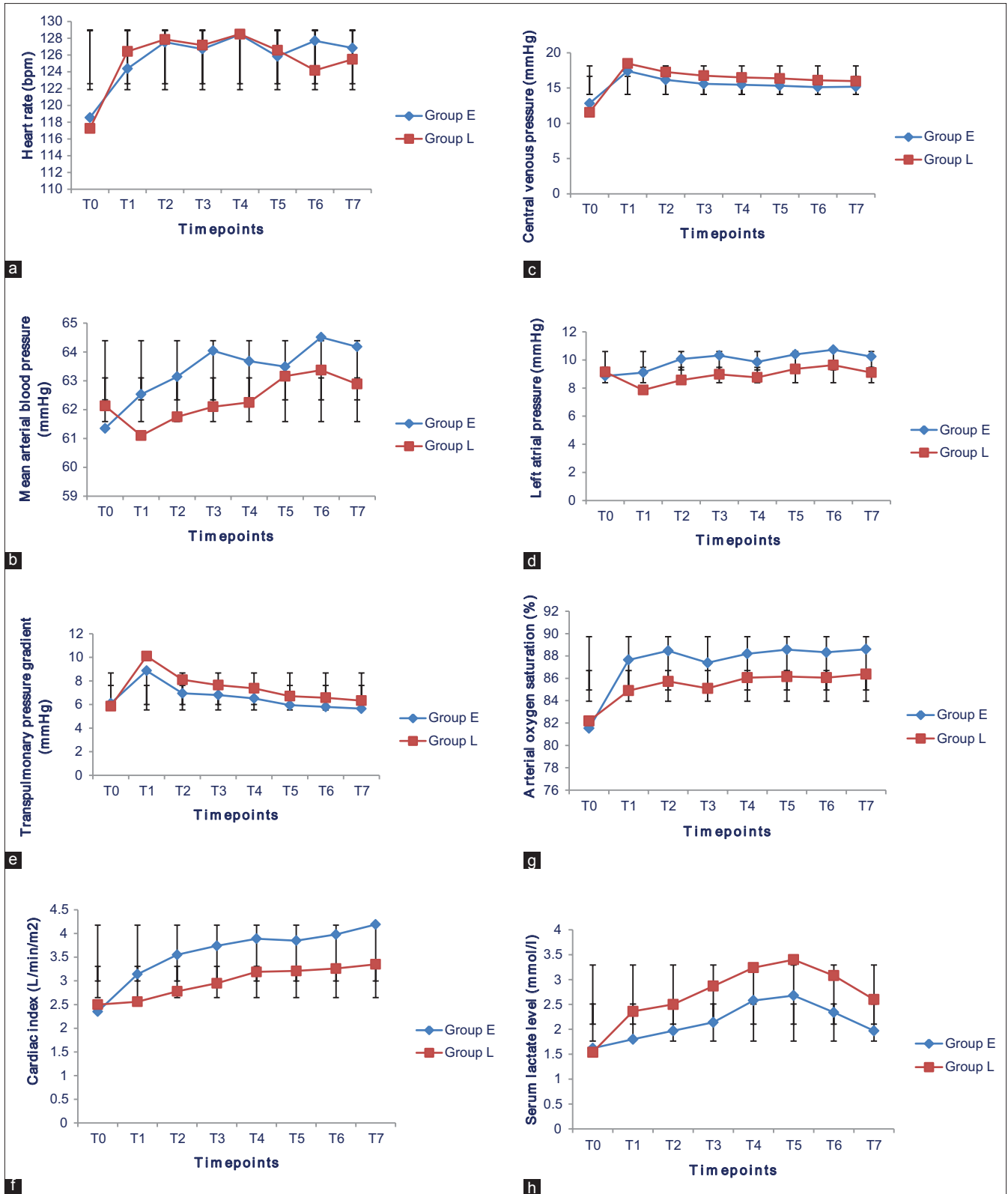
Figure 1: (a): Heart rate of patients; (b): Mean arterial blood pressure of patients; (c): Central venous pressure of patients; (d): Left atrial pressure of patients; (e): Transpulmonary pressure gradient of patients; (f): Cardiac index of patients; (g): Arterial oxygen saturation of patients; (h): Serum lactate level of patients. T0: Preoperative reading, T1: 15 min after weaning from cardiopulmonary bypass, T2: End of surgery, T3: 6 hours after Intensive Care Unit admission, T4: 12 h after Intensive Care Unit admission, T5: 24 h after Intensive Care Unit admission, T6: 36 h after Intensive Care Unit admission, T7: 48 h after Intensive Care Unit admission

Group E than Group L patients before weaning from CPB ($P < 0.001$) and not associated with hypotension.

However, the difference in the total milrinone dose was insignificant after weaning from CPB ($P = 0.194$) or in

the ICU ($P = 0.472$). The number of patients required for nitric oxide and nitroglycerine was lower in Group E than Group L ($P = 0.028$, $P = 0.031$, respectively), and also the required dose of nitric oxide and nitroglycerine was lower in Group E than Group L ($P = 0.011$, $P = 0.037$, respectively). All patients of the two groups required dopamine (the protocol in the cardiac center to use dopamine as the first inotropic agent to facilitate the weaning from CPB) during and after weaning from CPB, but the required dose of dopamine was lower in Group E than Group L ($P = 0.016$). The number of patients required for epinephrine was lower in Group E than Group L ($P = 0.033$). The duration of mechanical ventilation was shorter in the patient's Group E than Group L ($P = 0.011$). The urine output was higher in Group E than Group L patients ($P = 0.018$). The ICU

and hospital length of stay were shorter in the patient's Group E than Group L ($P = 0.013$, $P = 0.026$, respectively).

Discussion

The present study compared two different regimens of milrinone administration in pediatric patients undergoing Fontan procedure. The weaning off patients from CPB was easier in patients of Group E than Group L and the requirement for pharmacological support (nitric oxide, nitroglycerine, dopamine, and epinephrine) was lower in patients of Group E than Group L. The present study showed the following; (1) the cardiac index was higher in patients of Group E than Group L; (2) the increase in the postoperative central venous pressure was lower in patients of Group E than Group L, and this may be related to the decreased pulmonary vascular resistance that improved the

Variable	Group E (*n*=58)	Group L (*n*=58)	*P*
Lateral tunnel fenestrated Fontan	50	53	0.557
Lateral tunnel non-fenestrated Fontan	2	3	0.647
Extracardiac Fontan	6	2	0.271
Cardiopulmonary bypass time (min)	148.62±73.50	155.37±86.81	0.652
Aortic cross-clamping time (min)	72.16±21.39	77.58±24.30	0.204
Thorax closure time (min)	73.32±8.15	76.40±10.28	0.076
Milrinone dose (mg)			
Before weaning	1.46±0.24	0.96±0.36	0.001*
After weaning	0.72±0.03	0.74±0.05	0.194
ICU (dose/day)	14.21±4.63	14.90±5.62	0.472
Postoperative temporary pacemaker	6	8	0.776
Nitric oxide			
n	13	25	0.028
Dose (ppm)	28.78±4.93	31.23±5.35	0.011*
Nitroglycerine			
n	6	16	0.031*
Dose (µg/kg/min)	4.78±2.15	5.69±2.50	0.037*
Dopamine			
n	58	58	1.000
Dose (µg/kg/min)	6.37±1.45	7.10±1.77	0.016*
Epinephrine			
n	4	13	0.033*
Dose (µg/kg/min)	0.05±0.03	0.07±0.05	0.010
Packed RBC (unit=100 ml)	2.30±1.26	2.19±1.32	0.647
Fresh frozen plasma (unit=150 ml)	1.64±1.14	1.76±1.20	0.581
Platelet (unit=50 ml)	3.43±1.47	3.56±1.60	0.649
Cryoprecipitate (unit=15 ml)	2.50±1.30	2.42±1.22	0.732
Hemoglobin (g/dL)	15.86±5.63	15.57±5.90	0.787
Mechanical ventilation time (h)	14.55±2.75	16.00±3.32	0.011
Urine output (ml/kg/h)	2.79±1.25	2.25±1.18	0.018
Arrhythmia	-	-	
Pneumonia	-	-	
ICU length of stay (days)	7.32±2.19	8.37±2.33	0.013
Hospital length of stay (days)	16.75±3.61	18.28±3.70	0.026
Mortality	-	-	

Data are presented as mean±SD, n. *$P<0.05$: The comparison is significant between the two groups. Group E: Early milrinone group, Group L: Late milrinone group. Packed RBC: Packed red blood cells, ICU: Intensive Care Unit, SD: Standard deviation, *n*: number

blood flow to the lung; (3) the transpulmonary pressure gradient was lower in patients of Group E than Group L, and this indicates that the pulmonary vascular resistance was lower in Group E than Group L and this finding was reported by Howard et al.,[9] therefore, increasing the pulmonary blood flow;[10,11] (4) the left atrial pressure was higher in Group E than Group A, and this increased the filling pressure to left side of the heart and increased the cardiac index in Group E than Group L. Therefore, the increase in the postoperative oxygen saturation was higher in the patients of Group E than Group L. The improvement in the cardiac index and oxygenation led to an improvement of the tissue perfusion as indicated by a lower level of serum lactate and a higher urine output in the patients of Group E than Group L. Early milrinone was infused without bolus dose to avoid the possible problems such as hypotension related to bolus administration and it was found clinically that the early milrinone is more effective than the late milrinone with bolus dose. The total milrinone dose given before weaning from CPB was higher in patients of Group E, and this may lead to the improvement of outcomes with early milrinone administration. One study showed that infusion of milrinone at the beginning of CPB has a potent vasodilator effect and may be associated with improving tissues perfusion as indicated by lower serum lactate levels, higher urine output, and normal mixed venous oxygenation than administration of milrinone after CPB,[12] and that could be explained by study done by Möllhoff et al.[13] They showed that milrinone improved tissue perfusion and the postoperative oxygen transport to the tissue after cardiac surgery as a result of the increased cardiac output and vasodilatation associated with milrinone and the same results were shown by another study.[14]

A similar study in pediatric patients undergoing congenital corrective cardiac surgery showed that early milrinone increased the mean arterial blood pressure, central venous oxygen saturation, urine output and associated with decreased serum lactate level.[15] The good results with early uses of milrinone at the beginning of CPB may be related to the increased level of milrinone in the blood and its effect on the tissue perfusion during and after CPB[16] and other studies showed the same results.[6,7]

Chang et al.[8] reported that milrinone led to the increase in the cardiac index and a decrease in the pulmonary vascular resistance, right and left atrial pressures.

A retrospective analysis of high-risk patients who received milrinone before CPB initiation were weaned easily from CPB and associated with a significant decrease in the pulmonary artery pressure and significant improvement of ventricular function.[17,18]

Other studies showed that the anti-inflammatory properties of milrinone prevent the development inflammatory mediators and acidosis that may affect the pulmonary vascular resistance.[19-21]

Garofalo et al.[22] showed the ventricle had significantly higher stiffness immediately after Fontan operation and milrinone improves the pulmonary circulation by increasing myocardial relaxation.

Other studies found that the use of milrinone after CPB in pediatric patients undergoing Fontan procedure has no effect on the oxygen saturation, elevated pulmonary vascular resistance, central venous pressure, left atrial pressure, transpulmonary pressure gradient, and clinical outcomes after Fontan and the possible causes, (1) a limited amount of milrinone could enter into the pulmonary circulation at the initial stage as a result of a significant shunt to the systemic circulation through the fenestration, secondary-to-high pulmonary vascular resistance, and a lower concentration of milrinone in the pulmonary vascular wall; (2) the optimum concentration in the blood requires maintained infusion to be effective.[3,6,23-26]

Other studies showed that the plasma concentration of a continuous infusion without a bolus reached the same level after 1 h as the concentration in patients who received continuous infusion initiated by a loading dose.[27-29]

Contrary to the result of the present study, Malec et al.[30] reported that milrinone infusion (0.25–0.75 µg/kg/min) after CPB, improved the outcome after Fontan procedure.

The present study recognizes some limitations such as the serum level of milrinone was not measured, as the kits for measurement were not available in the laboratory.

Conclusion

Early use of milrinone in patients undergoing Fontan procedure facilitated the weaning from CPB, decreased the elevation in the central venous pressure, transpulmonary gradient pressure, and the requirement for pharmacological support. Furthermore, it increased the cardiac index and arterial oxygen saturation.

Conflicts of interest

There are no conflicts of interest.

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