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Research Article

Effects of olprinone on hemodynamics and oxygen delivery in pediatric cardiac surgery: Magnitude of effects and comparison to milrinone

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KEYWORDS

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Abstract *Background and objectives:* Our study seeks to evaluate the effects of olprinone on hemodynamics and oxygen delivery on weaning from cardiopulmonary bypass (CPB) and to compare the effects of olprinone and milrinone.
Methods: We retrospectively reviewed 50 pediatric patients administered either olprinone or milrinone on weaning from CPB during cardiac surgery. At 0, 15, 30, 60, 90, and 120 minutes (min) after separation from CPB, we collected data on hemodynamics and oxygen delivery. At the same time points, we also recorded the doses of cardiovascular-acting drugs used concomitantly. We analyzed differences among measurement points by one-way ANOVA and differences between two agents groups by two-way ANOVA.
Results: Olprinone increased systolic blood pressure (sBP) at 120 min in biventricular repair (BV) and from 90 min in Fontan-type operation (FO). Olprinone produced significant stepwise tapering of dopamine from 60 min and dobutamine from 90 min in BV. For BV, olprinone significantly increased central venous oxygen saturation from 30 min; oxygen excess factor at 30 and 120 min; and cerebral tissue oxygen index from 30 min, except at 60 min. Except for a significant increase in sBP and significant tapering of DOA dose at 120 min in BV, milrinone had no effect on any parameters in either type of operation. Comparisons of the two agent groups showed no significant difference in any parameters.

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Conclusion: Olprinone stabilizes circulation and improves oxygen delivery during BV pediatric cardiac surgery. While olprinone may have stronger effects than milrinone in BV, the two agents were comparable for FO.

1. Introduction

Several studies attest to the usefulness of milrinone in stabilizing circulation or improving outcomes in pediatric cardiac surgery. Chang et al. report that administering milrinone in neonates with low cardiac output syndrome (LOS) after cardiac surgery significantly lowers systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) while improving cardiac index (CI) [1]. Bailey et al. demonstrated that a loading dose of milrinone resulted in an 18% mean increase in CI after separation from cardiopulmonary bypass (CPB) during cardiac surgery in children aged from 3 to 22 months [2]. A large multi-center study in North America (the PRIMACORP study) showed that high-dose milrinone significantly reduced mortality and incidence of LOS after pediatric cardiac surgery. The PRIMACORP study also showed that even low-dose milrinone tends to reduce mortality and LOS development, although not at statistically significant levels [3]. The efficacy of milrinone in the field of congenital heart disease is now well recognized.

Olprinone, another phosphodiesterase-3 (PDE-3) inhibitor developed in Japan in 1996, is currently available for clinical use. Several studies show olprinone significantly reduces SVR and significantly increases CI during or after coronary artery bypass graft or valve surgery in adults [4–7]. However, there is little current data on the potential effects of olprinone on hemodynamics and oxygen delivery for pediatric cardiac surgery. The present study seeks to evaluate the effects of olprinone on these parameters and to compare olprinone to milrinone on weaning from CPB.

2. Methods

2.1. Materials

We retrospectively reviewed pediatric patients administered PDE-3 inhibitors, either olprinone or milrinone, on weaning from CPB during cases of cardiac surgery performed at the Tokyo Women's Medical University Hospital from February 2009 to December 2010. Our policies call for administering PDE-3 inhibitors in patients with congestive heart failure (CHF) or pulmonary hypertension (PH) preoperatively and in patients regarded to be at high risk of LOS postoperatively. Our infusion standards call for initiating continuous infusion, either olprinone (at 0.3 μg/kg/min) or milrinone (at 0.5 μg/kg/min) with no loading dose immediately after the release of the aortic cross-clamping or, in the absence of aortic cross-clamping, immediately upon completion of surgical procedures. The study excluded all patients who failed to meet these standards in any way. The study also excluded patients exhibiting any change in infusion rates by the end of data collection (120 minutes (min) after separation from CPB). This study was approved by the institutional ethics committee with a waiver of the requirement to obtain written informed consent from parents or guardians of the studied patients.

2.2. Anesthesia

General anesthesia was induced either by inhalation of sevoflurane or intravenous midazolam. Anesthesia was maintained through a combination of inhaled sevoflurane and intravenous fentanyl. Our standards of anesthesia allow administration of high-dose fentanyl (minimum of 50–100 μg/kg) to patients with moderate to severe PH preoperatively and to patients judged to be at high risk of LOS postoperatively. We administered lower-dose fentanyl (less than 50 μg/kg) to the remaining patients. We confirmed that all patients in this study met these standards.

2.3. Hemodynamic data

We gathered hemodynamic data, including blood pressure (BP), heart rate (HR), and central venous pressure (CVP) at 0 (completion of separation from CPB), 15, 30, 60, 90, and 120 min after separation from CPB. Since both the normal range and the targeted values of these parameters varied with the patients' age and pathophysiology, we determined the changes from values at separation from CPB as percentage values.

We recorded the doses of the cardiovascular active drugs used concomitantly at the same time points at which hemodynamic data were collected (0, 15, 30, 60, 90, and 120 min after separation from CPB) and calculated the catecholamine index at each time point by applying the following formula:

$$\begin{aligned} \mathit{Catecholamine\,index} = {} & \mathit{dopamine\,dose} + \mathit{dobutamine\,dose} \\ & + 100 \times \mathit{noradrenaline\,dose} \\ & + 100 \times \mathit{adrenaline\,dose} \\ & (\mathit{doses\,of\,all\,agents\,are\,shown\,in\,\mu g/kg/min}) \end{aligned}$$

2.4. Oximetric data

We gathered venous oxygen saturation ($ScvO_2$) measured via a PediaSat central venous catheter (Edwards Lifesciences, USA) placed in the superior vena cava at 0, 15, 30, 60, 90, and 120 min after separation from CPB and calculated the oxygen excess factor, omega (Ω), by substituting into the following formula the values for $ScvO_2$ and oxygen saturation on pulse oximetry (SpO_2) at each measurement point.

$$\Omega = SpO_2/(SpO_2 - ScvO_2)$$

We routinely monitored cerebral tissue oxygen index (TOI) by NIRO (NIRO 300; Hamamatsu Photonics, Japan) for all patients who underwent cardiac surgery. For most (but not all) cases during the study period, we also monitored cerebral tissue oxygen saturation (rSO_2) by INVOS (INVOS 5100; Somanetics, USA). We gathered data on TOI and rSO_2 at each measurement point.

2.5. Statistical analysis

Data are expressed as mean plus–minus standard deviation or median with range. Between the olprinone group and the milrinone group for either operation, and between biventricular repair cases and Fontan-type operation cases among either agent group, we applied an unpaired *t*-test and Chi-square test to compare data on patient demographics and preoperative examinations. We applied one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test to analyze differences between values at separation from CPB in hemodynamic and oximetric parameters. To analyze differences in hemodynamic and oximetric parameters between the olprinone group and milrinone group, we used two-way ANOVA followed by Bonferroni correction for multiple comparisons. A $p < 0.05$ was considered statistically significant.

3. Results

Our study enrolled 50 patients who met our standards for PDE-3 inhibitor infusion. Of these patients, 29 were administered olprinone and 21 administered milrinone. In the olprinone group, 19 patients underwent biventricular repair; 10 underwent the Fontan-type operation. In the milrinone group, 14 underwent biventricular repair and 7 the Fontan-type operation.

3.1. Demographic data and data on both patient preoperative cardiac function and pulmonary condition

We collected data on cardiac function and pulmonary condition at the most recent preoperative echocardiography or cardiac catheterization. Table 1 summarizes this data and the demographic data. We observed no significant differences between the olprinone group and milrinone group in any parameter for either operation. Likewise, we observed no significant differences between data for the biventricular repair cases and data for Fontan-type operation cases between the agent groups.

3.2. Changes in hemodynamic parameters

Olprinone did not affect HR or diastolic BP in either the biventricular repair group or in the Fontan-type operation group. Systolic BP was significantly increased at 120 min after separation from CPB in the biventricular repair group and from 90 min after separation from CPB in the Fontan-type operation group. In the biventricular repair group alone, CVP was significantly elevated from 90 min after weaning from CPB (Fig. 1).

Milrinone had no effect on parameters in either operation group, with the exception of a significant increase in systolic BP at 120 min after weaning from CPB in the biventricular repair group (Fig. 1).

Comparisons of the two agents showed no differences in either parameter for either operation (Fig. 1).

3.3. Changes in oximetric parameters

No PediaSat catheter was used in 5 cases in the olprinone group (3 biventricular repair and 2 Fontan-type operation) and 4 cases in the milrinone group (2 for each procedure type). From rSO_2 analysis, we excluded 10 cases in the olprinone group (9 biventricular repair and 1 Fontan-type operation) and all but 6 Fontan-type cases in the milrinone group. This was done because no probe had been applied or due to the unreliability suggested by extremely high values (exceeding 95%). We also excluded from TOI analysis 8 cases—5 in the olprinone group (4 biventricular repair and 1 Fontan-type operation) and 3 in the milrinone group (2 biventricular repair and 1 Fontan-type operation)—due to unstable TOI values likely attributable to unstable attachment of probes to the patient forehead.

Olprinone significantly increased $ScvO_2$ from 30 min after weaning from CPB and Ω at 30 min and 120 min after weaning from CPB. Additionally, olprinone increased TOI starting 30 min, except at 60 min, after weaning from CPB in the biventricular repair group. The agent had no effect on any parameters for the Fontan-type operation group (Fig. 2).

Milrinone did not affect parameters in either type of operation (Fig. 2).

Comparisons of the two agents indicate that olprinone produced a significantly greater increase from baseline (0 min) for both $ScvO_2$ and Ω at 30 min and 120 min after weaning from CPB in biventricular repair cases, but no significant difference in any parameters for Fontan-type operation cases (Fig. 2).

3.4. Infused doses of other cardiovascular drugs administered concomitantly

All patients in our study received dopamine and nitroglycerine. Dobutamine was administered to 19 patients in the olprinone group, including 14 biventricular repair cases and 5 Fontan-type operation cases, and to 12 patients in the milrinone group, including 9 biventricular repair cases and 3 Fontan-type operation cases. The frequency of use of these drugs was comparable for the olprinone group and milrinone group for both types of operations. These drugs aside, only 3 biventricular repair cases in the olprinone group were administered isoproterenol, up to a maximum dose of 0.01 μg/kg/min, due to high-degree atrioventricular block. Two of the 3 patients received a very small dose of the agent (up to 0.005 μg/kg/min) for a brief duration (approximately 30 min).

In the biventricular repair group but not in the Fontan-type operation group, olprinone produced significant stepwise tapering of dopamine from 60 min, dobutamine from 90 min, and of the catecholamine index starting 60 min after weaning from CPB. In contrast, milrinone reduced dopamine only at 120 min after weaning from CPB (Fig. 3). Neither agent significantly affected the dose of the other cardiovascular-acting drugs in the Fontan-type operation group (Fig. 3).

Comparisons of the two agents showed no differences in the doses of the other drugs used concomitantly at same time point (Fig. 3).

4. Discussion

To the best of our knowledge, this study is the first to investigate the effects of olprinone on both hemodynamics and oxygen delivery during pediatric cardiac surgery. Our study showed that olprinone is effective in stabilizing circulation and improving oxygen delivery after weaning from CPB in

Table 1 Data on patient demographics and preoperative examinations.

	Biventricular repair			Fontan-type operation		
	Olprinone	Milrinone		Olprinone	Milrinone	
Age (mo)	11.0 (2–67)	17.5 (3–143)	NS	23.0 (11–44)	24.0 (8–27)	NS
Gender (M/F)	11/8	11/3	NS	3/7	4/3	NS
BW (kg)	6.5 (3.8–23.0)	9.3 (5.5–33.8)	NS	11.0 (7.0–15.0)	10.0 (6.6–13.6)	NS
Diagnosis	VSD 10, TOF 3, AR 1, Cortriatrium 1, ASD 2, IAA with VSD 2	VSD 5, TGA 2, DORV 2, ASR 1, MS 1, PS 1, TOF 1, ASD 1		SRV 3, TA 4, PPA 1, small LV 1, DORV 1	SRV 2, TA 3, Ebstein 1, DORV 1	
Dominant ventricle (L/R/B)				5/4/1	4/3/0	
AVVR (none/trivial-mild/moderate)				5/3/2	1/6/0	
EDVI (cm^3/m^2)	130.0 ± 55.4	180.0 ± 91.3	NS	155.5 ± 44.6	143.1 ± 44.2	NS
EF (%)	60.0 ± 7.5	61.4 ± 8.4	NS	55.4 ± 13.5	54.1 ± 11.2	NS
EDP (mmHg)	8.4 ± 4.0	10.1 ± 4.0	NS	9.9 ± 3.4	9.3 ± 4.2	NS
PAP (mmHg)				14.8 ± 3.6	14.5 ± 3.2	NS
PA index				237 ± 86	220 ± 78	NS
Rp (Wood unit)				2.4 ± 0.6	2.2 ± 0.5	NS

mo: months old, M: male, F: female, NS: not significant, BW: body weight, VSD: ventricular septal defect, TOF: tetralogy of Fallot, AR: aortic regurgitation, ASD: atrial septal defect, IAA: interrupted aortic arch, TGA: transposition of the great arteries, DORV: double outlet from right ventricle, ASR: aortic stenosis with aortic regurgitation, MS: mitral stenosis, PS: pulmonary stenosis, SRV: single right ventricle, TA: tricuspid atresia, PPA: pure pulmonary atresia, LV: left ventricle, L/R/B: left/right/balanced, AVVR: atrio-ventricular valvular regurgitation, EDVI: end-diastolic volume index, EF: ejection fraction, EDP: end-diastolic pressure, PAP: pulmonary artery pressure, Rp: pulmonary vascular resistance

We found no significant difference between the two agent groups for either type of operation.

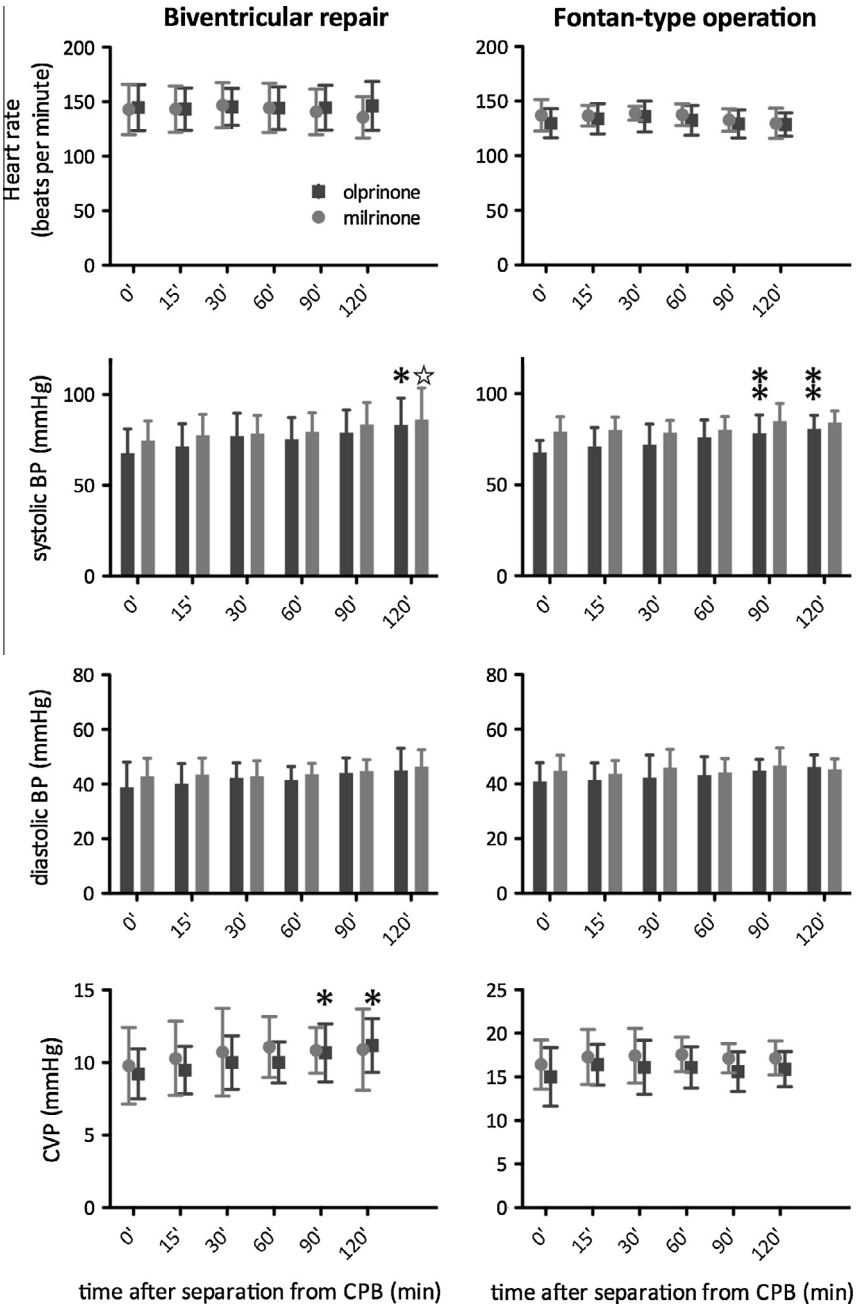

Figure 1 Effects of olprinone and milrinone on hemodynamic parameters. Olprinone produced significant increases in sBP at 120 min for biventricular repair (*$p < 0.05$ vs. Olp 0′) and from 90 min for the Fontan-type operation (⁂$p < 0.05$ vs. Olp 0′ and Olp 15′). CVP was elevated from 90 min only for biventricular repair (*$p < 0.05$ vs. Olp 0′). Milrinone did not affect parameters in either operation group, except for a significant increase in sBP at 120 min for biventricular repair ($^{\star}p < 0.05$ vs. Mil 0′). Comparisons of the two agents showed no differences in any of the parameters for either operation.

cases of biventricular repair. We found that olprinone had similar results in stabilizing circulation and improving oxygen delivery in Fontan-type operations, but not at statistically significant levels.

A previous study evaluated the effects of olprinone and milrinone on CI, SVR, and PVR after pediatric cardiac surgery in the ICU by the thermodilution technique, showing that both olprinone and milrinone prevented CI deterioration without affecting HR and that both agents significantly reduced SVR, while milrinone reduced PVR more potently than olprinone [8]. Although our study did not measure cardiac output directly, we evaluated $ScvO_2$ and Ω. Li et al. report that both $ScvO_2$ and Ω correlate significantly with systemic blood flow as well as oxygen delivery in neonates after the Norwood operation [9]. In particular, they observed a good correlation between Ω and oxygen delivery [9]. Two studies set in ICUs, one of newborns and infants excluding cases of brain injury [10] and the other of children following corrective surgery for non-cyanotic congenital heart disease [11], indicate that TOI correlates moderately with SvO_2. Tortoriello et al. showed

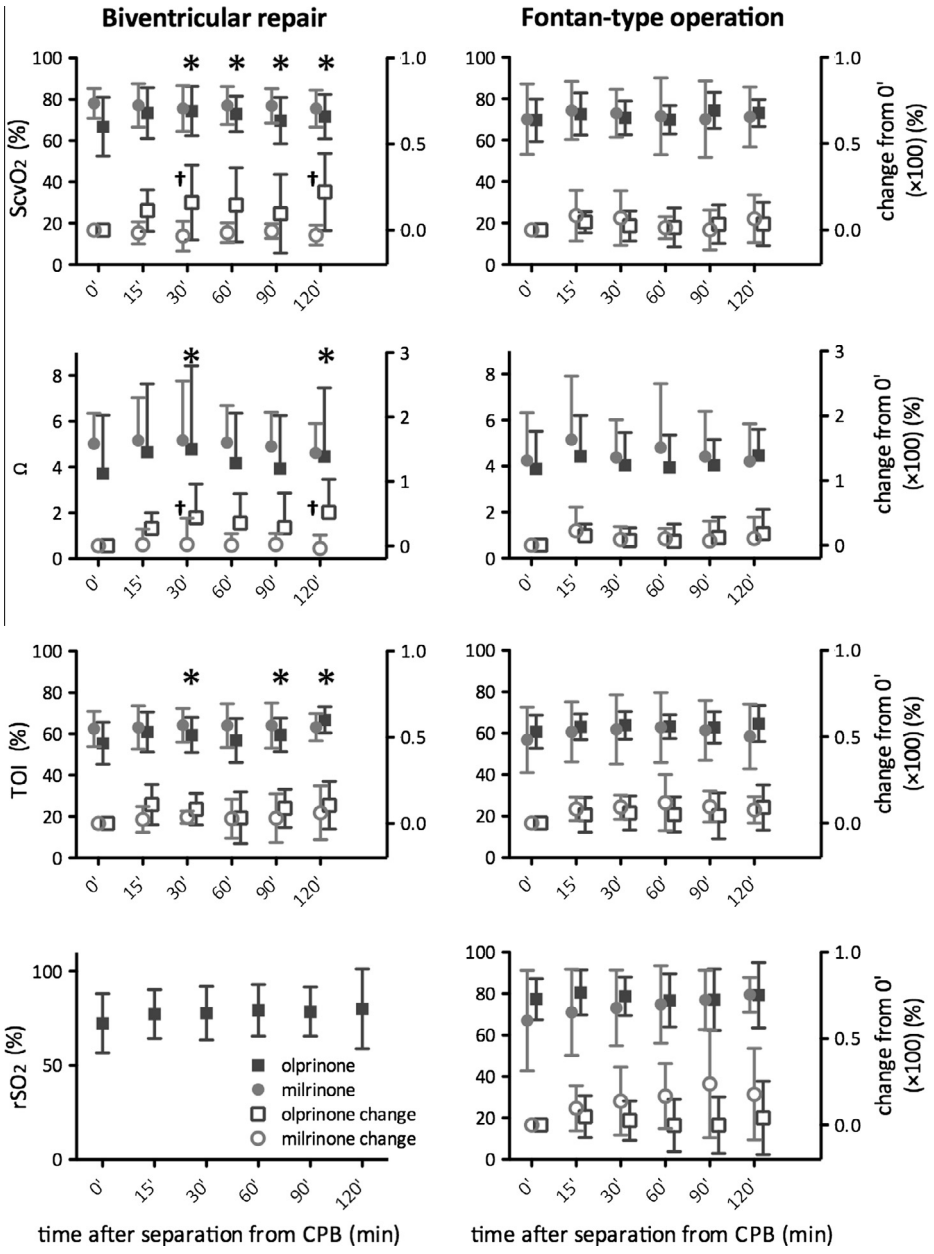

Figure 2 Effects of olprinone and milrinone on oximetric parameters. Olprinone significantly increased $ScvO_2$ from 30 min and Ω at 30 min and 120 min after weaning from CPB (*$p < 0.05$ vs. Olp 0′). From 30 min (except at 60 min), it also increased TOI in cases involving biventricular repair (*$p < 0.05$ vs. Olp 0′), while the agent had no effect on any parameters for the Fontan-type operation. Milrinone did not affect any parameters for either type of operation. Comparisons of the two agents showed a significantly greater increase in $ScvO_2$ and Ω at 30 min and 120 min in the olprinone group in biventricular repair cases ($^{\dagger}p < 0.05$ Olp vs. Mil), but no significant difference in any of the parameters for the Fontan-type operation.

that rSO_2 correlates moderately with SvO_2 in duration from after weaning from CPB to 6 hours after admission to ICU in cases of pediatric cardiac surgery [12].

In our study, olprinone in the biventricular repair group increased systolic BP with no effects on HR. Before the increase in systolic BP, we observed tapering of the concomitantly used dopamine dose and increases in $ScvO_2$, Ω, and TOI concurrent with achievement of effective blood concentrations of olprinone. A previous study involving the 13 subjects enrolled in both the current and previous studies confirmed that the olprinone infusion regimen achieved effective plasma olprinone concentrations within 30 min after separation from CPB (or within 60 min after the initiation of infusion) [13]. We did not set restrictive criteria for tapering in doses of the concomitantly used catecholamines. In principle, doses were tapered once the targeted values in circulatory parameters (given the patient's age and pathophysiology) had been achieved and once transesophageal echocardiography confirmed normal ventricular contraction. Thus, olprinone must induce an increase in CI and reductions in SVR, enabling tapering in doses

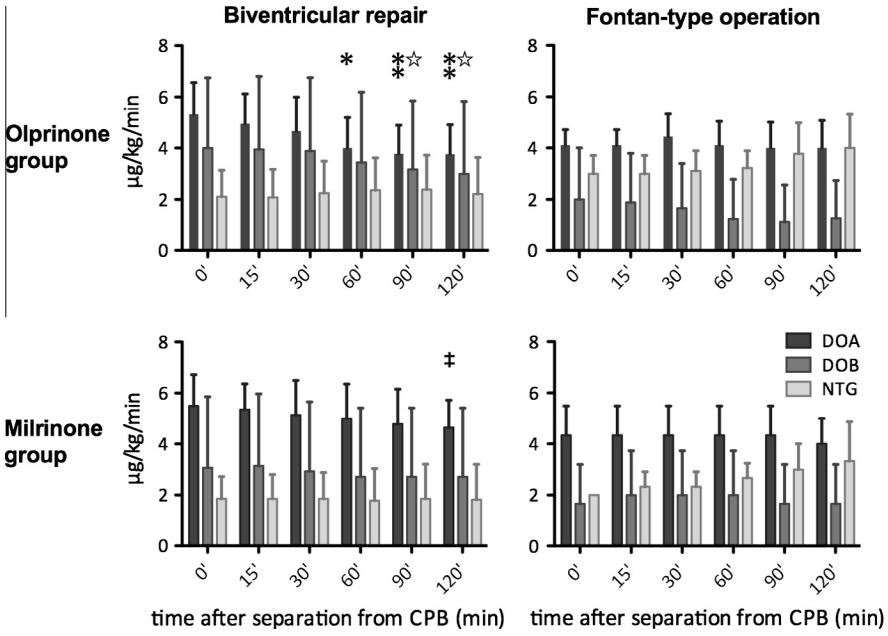

Figure 3 Doses of concomitantly used inotropes and vasodilator. Olprinone produced significant stepwise tapering of both dopamine from 60 min (*$p < 0.05$ vs. DOA 0′ and 15′, ‡$p < 0.05$ vs. DOA 0′, 15′, and 30′), dobutamine from 90 min (☆$p < 0.05$ vs. DOB 0′, 15′, and 30′), and the resulting catecholamine index from 60 min after weaning from CPB only for biventricular repair. Milrinone reduced dopamine doses only at 120 min (†$p < 0.05$ vs. DOA 0′). Neither agent affected the doses of other cardiovascular-acting drugs for the Fontan-type operation. Comparisons of the two agents showed no difference in doses of the other drugs used concomitantly at any time point.

of the concomitantly used catecholamines, while improving oximetric parameters and maintaining hemodynamic parameters. CVP rose in biventricular repair patients starting at around 90 min after weaning from CPB. In approximately two-thirds of the patients in this group, the sternum was closed from 60 to 90 min after weaning from CPB. In the remaining patients, the sternum was closed at a time point exceeding 90 min after weaning from CPB. While the elevation in CVP was small and temporary in most the patients, it nonetheless appeared to persist for a non-negligible duration.

In our series, rSO_2 exceeded TOI. These parameters varied widely from case to case. Dullenkopf et al. report that absolute values of rSO_2 and TOI vary widely among individuals, even at baseline [14]. They also demonstrate that rSO_2 values, particularly with pediatric sensors, are significantly higher than TOI values [14]. These findings suggest our data on cerebral rSO_2 and TOI are sufficiently reliable to estimate systemic blood flow and oxygen delivery indirectly.

We also observed the abovementioned trends in hemodynamic and oximetric parameters during olprinone administration in cases of Fontan-type operations, but not at statistically significant levels. In Fontan physiology, selectively reducing PVR is a key factor in increasing CI and oxygen delivery, differing in this respect from biventricular circulation. A study has demonstrated that olprinone reduces PVR insignificantly compared to placebo [8]. Moreover, in our series, patients in the Fontan-type operation group were more likely to have small ejection fraction and elevated end-diastolic pressure in the ventricle than patients in the biventricular repair group. These may account for the less potent effects of olprinone on circulation and oxygen delivery in Fontan-type operations.

We observed similar but weak trends during milrinone administration for both types of operations. Although we did not confirm effective blood concentrations for milrinone, our infusion rate was the same as in the previous study comparing the effects of olprinone and milrinone on circulation after pediatric cardiac surgery [8]; additionally, our infusion rate exceeded the rate used for low-dose cases in the PRIMACORP study, even when accounting for the loading dose used in the PRIMACORP study [3]. Demographic data and data for both patient preoperative cardiac function and pulmonary condition were comparable for the two agent groups. Comparisons of the two agents indicated significantly greater improvement in two oximetric parameters, $ScvO_2$ and Ω, in the olprinone group during biventricular repair. In addition to early stepwise tapering of concomitantly used cathecolamines in the olprinone group, this suggests that olprinone might be more potent in stabilizing circulation and improving oxygen delivery in biventricular repair. The two agents were equally effective for Fontan-type operation cases.

4.1. Limitations

Our study is subject to several limitations. First, it was conducted in retrospective manner. Second, the sample size was small. Statistical power analysis failed to reach 0.8 for any oximetric parameter but exceeded 0.8 for all increases in hemodynamic parameters and for the tapering of the DOA dose for biventricular repair in the olprinone group. In addition, the study subjects did not have uniform backgrounds. Age, diagnosis, pathophysiology, and severity of illness varied widely. Moreover, surgical insults, including operation time, CPB time, and aortic cross-clamping time, differed case by case.

These factors may affect the magnitude of the effects of olprinone or milrinone on circulation and oxygen delivery. Ideally, these factors should be controlled in a study with a small sample size. Lastly, MUF was applied to the majority of the cases in our study. MUF may remove various inflammatory mediators such as cytokines [15] and may subsequently improve patient hemodynamic states [16]. Due to the absence of a control group, our study was unable to clearly distinguish the effects of MUF on hemodynamics and oxygen delivery from the effects of PDE-3 inhibitors.

In summary, olprinone stabilized circulation and improved oxygen delivery in cases of biventricular repair. The magnitude of olprinone's effects may exceed milrinone for biventricular repair cases and may equal milrinone for Fontan-type cases.

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