Efficacy and Safety of Milrinone in Preventing Low Cardiac Output Syndrome in Infants and Children After Corrective Surgery for Congenital Heart Disease

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Background—Low cardiac output syndrome (LCOS), affecting up to 25% of neonates and young children after cardiac surgery, contributes to postoperative morbidity and mortality. This study evaluated the efficacy and safety of prophylactic milrinone in pediatric patients at high risk for developing LCOS.

Methods and Results—The study was a double-blind, placebo-controlled trial with 3 parallel groups (low dose, 25-μg/kg bolus over 60 minutes followed by a 0.25-μg/kg per min infusion for 35 hours; high dose, 75-μg/kg bolus followed by a 0.75-μg/kg per min infusion for 35 hours; or placebo). The composite end point of death or the development of LCOS was evaluated at 36 hours and up to 30 days after randomization. Among 238 treated patients, 25.9%, 17.5%, and 11.7% in the placebo, low-dose milrinone, and high-dose milrinone groups, respectively, developed LCOS in the first 36 hours after surgery. High-dose milrinone significantly reduced the risk the development of LCOS compared with placebo, with a relative risk reduction of 55% ($P=0.023$) in 238 treated patients and 64% ($P=0.007$) in 227 patients without major protocol violations. There were 2 deaths, both after infusion of study drug. The use of high-dose milrinone reduced the risk of the LCOS through the final visit by 48% ($P=0.049$).

Conclusions—The use of high-dose milrinone after pediatric congenital heart surgery reduces the risk of LCOS. **(*Circulation*. 2003;107:996-1002.)**

Key Words: cardiac output ■ heart defects, congenital ■ pediatrics ■ mortality

Several studies have documented the predictable fall in cardiac output, referred to as low cardiac output syndrome (LCOS), which occurs after congenital heart surgery. In 1975, Parr et al[1] reported that nearly 25% of young children had a cardiac index of <2.0 L/min per m^2 postoperatively as measured by dye dilution, and this finding was a predictor of acute cardiac death. Similarly, Wernovsky et al[2] reported that 25% of neonates with transposition of the great arteries who underwent an arterial switch operation had a decline in cardiac index to <2.0 L/min per m^2, typically occurring between 6 and 18 hours after surgery. This fall in cardiac index was associated with an elevated systemic vascular resistance of ≈25% and a rise in pulmonary vascular resistance of nearly 40% from baseline values. Other recent reports document similar hemodynamic[3,4] and respiratory[5] findings after surgery in neonates and young infants.

Causes of LCOS after cardiac surgery are multifactorial, including myocardial ischemia during aortic cross clamping, the effects of cardioplegia, activation of the inflammatory and complement cascades, and alterations in systemic and pulmonary vascular activity.[2] Residual cardiac lesions, even when minor, may also adversely impact the postoperative course.

Because LCOS is common and contributes to postoperative morbidity and mortality, prevention of this predictable hemodynamic deterioration may have significant implications for clinical outcome. Preventing LCOS may impact hospital length of stay and may decrease the risk for postsurgical, nosocomial, and central nervous system complications.

Traditionally, inotropic agents and vasodilators have been used to enhance tissue perfusion and facilitate postoperative recovery.[6–10] The use of catecholamines has several drawbacks, including increased myocardial oxygen consumption, heart rate, afterload, and risk of arrhythmia. β-Adrenergic receptors may be downregulated as well in patients with preexisting heart failure. Because of these potential limita-

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tions, phosphodiesterase inhibitors such as amrinone[11] and milrinone[8] have been increasingly used in the postoperative period.[12] In studies performed with patients having low cardiac index, phosphodiesterase inhibitors increased cardiac output, reduced systemic and pulmonary vascular resistance, and decreased filling pressures.[8,9] Because LCOS occurs frequently in pediatric patients after congenital heart surgery, the prophylactic use of a positive inotropic and vasodilatory agent, such as milrinone, may improve cardiac function and lower the risk of morbidity and mortality. The purpose of the PRIMACORP trial (PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics) was to evaluate the efficacy and safety of the prophylactic use of milrinone in pediatric patients at high risk of developing LCOS after cardiac surgery.

Methods

PRIMACORP was a multicenter, randomized, double-blind, placebo-controlled trial using 3 parallel treatment groups of pediatric patients undergoing cardiac surgery. Thirty-one centers in North America participated in this study. Each site participated in the study only after approval by its institutional review board. Before enrollment, written informed consent was obtained from each patient's parent or guardian. The details of the methods and study design have been previously reported.[13] Eligible patients were 6 years of age or younger without preoperative LCOS who were undergoing biventricular repair of certain cardiac lesions involving cardiopulmonary bypass (Table). Exclusion criteria included a body weight of <2 kg, prematurity (birth <36 weeks postconceptual age), renal dysfunction (creatinine ≥ 1.5 mg/dL 48 hours before surgery), and LCOS or hypotension on arrival to the intensive care unit from the operating room. Patients were randomly assigned, in a 1:1:1 ratio within 90 minutes after arriving in the intensive care unit, to receive either low-dose intravenous milrinone (25 μg/kg bolus over 60 minutes followed by a 0.25 μg/kg per min infusion for 35 hours), high-dose intravenous milrinone (75 μg/kg bolus over 60 minutes followed by a 0.75 μg/kg per min infusion for 35 hours), or placebo. The physicians were given the option to discontinue study drug between 24 and 36 hours for patients who appeared clinically well. Baseline catecholamines were administered at the discretion of the physician; a combined inotropic drug score was calculated for each patient to account for differences in baseline medications among treatment groups.[2,14]

The primary end point was a composite variable consisting of death or the development of LCOS requiring additional pharmacological or other support administered within the first 36 hours after receiving study drug. LCOS was defined as clinical signs or symptoms (eg, tachycardia, oliguria, poor perfusion, or cardiac arrest) with or without a widened arterial-mixed venous oxygen saturation difference or metabolic acidosis.[13] Additional pharmacological or other support was defined as mechanical support of the circulation (eg, extracorporeal life support), an increase in the amount of pharmacological support relative to baseline ($\geq$100% over baseline), the administration of a new, open-label inotropic agent, or other interventions (eg, mechanical pacing) specifically to treat LCOS. Patients who received additional therapies not aimed at treating LCOS were not considered reaching the primary end point. Secondary end points included the evaluation of the composite end point of death or development of LCOS in the interval between 36 hours after initiation of study drug and the final visit (up to 30 days after randomization), the duration of mechanical ventilation, length of hospital stay, total urine output, and creatinine clearance at the end of study drug administration. Hemodynamic parameters (heart rate, systolic and diastolic blood pressure, and right and left atrial pressure), if available, were recorded at the start of study drug infusion and every 4 hours through 36 hours. Systolic and diastolic blood pressure alterations were analyzed as a percent change from baseline. Arterial and venous cooximetry as well as lactate levels were obtained at baseline and every 4 hours for 36 hours.

The steering committee developed the protocol and provided academic leadership for the overall conduct of the trial. A blinded clinical end point committee, using standard methods established by a steering committee, adjudicated patient end point–related data.[13] An independent data and safety monitoring board was used.

The primary and secondary end points were analyzed using a pairwise comparison test (t test) at the 0.025 and 0.05 levels, respectively. The secondary end point had no adjustments of the probability value for multiple comparisons. Categorical variables were analyzed using a χ^2 test, and continuous variables were analyzed by ANOVA t tests with treatment and physician as main effects in the model. Geometric means were used for analysis of variables with extreme outliers. Log-rank and Kaplan-Meier curves were used to compare the time to development of LCOS or death between low- and high-dose milrinone.

Results

Of 242 enrolled patients, 238 patients received study medication. Because of major protocol violations, the per-protocol population consisted of 227 patients. After the completion of study drug infusion, 13 patients in the per-protocol population received open-label milrinone; data for these patients were not included in the secondary end point of LCOS through the follow-up visit. A total of 5 patients were lost to follow-up after hospital discharge (Figure 1). The per-protocol population (n=227) ranged in age from 2 days to 6.9 years (median, 3 months). There were no statistically significant differences among the 3 treatment groups with respect to demographic variables, surgical procedures, intraoperative support times, and baseline inotropic support (Table).

Primary End Point

No patients died during administration of study drug; therefore, the primary end point was based solely on the occurrence of LCOS requiring treatment. The use of high-dose milrinone significantly reduced the risk of the development of LCOS compared with that of placebo in all treated patients ($P=0.023$, relative risk reduction 55%) and in the per-protocol population ($P=0.007$, relative risk reduction 64%, Figure 2). There was a statistically insignificant trend toward a lower incidence of the primary end point with low-dose milrinone.

Secondary End Points

Two patients (0.8%) who underwent surgery for complete atrioventricular canal died after completion of study drug administration; both deaths were deemed by their physicians to be unrelated to study drug (aspiration pneumonia on postoperative day 5 and multisystem organ failure on postoperative day 13). There was a significant reduction in the composite variable (death or the development of LCOS) by the final visit, with the high-dose milrinone group resulting in a 48% relative risk reduction ($P=0.049$). The time course to the development of LCOS is shown in Figure 3.

There were no differences in the diagnostic features of LCOS between treatment groups. The clinical features in the 44 patients with LCOS included 72.7% with cool extremities, 54.5% with oliguria, 31.8% with tachycardia, and 2.3% (1 patient) with a cardiac arrest; 45.5% had a widened ($\geq$30%) arterial-mixed venous oxygen difference, and 22.7% had a

Patient Characteristics (n=227)

	Placebo (n=75)	Low Dose (n=79)	High Dose (n=73)
Demographics			
Age, mo	8.3±14.8	5.9±10.2	8.6±16.5
Weight, kg	6.1±4.1	5.7±3.3	5.9±4.0
Male, %	48.0	60.8	53.4
Female, %	52.0	39.2	46.6
White, %	69.3	78.5	68.5
African-American, %	20.0	11.4	13.7
Other, %	10.7	10.1	17.8
Surgery			
Repair of tetralogy of Fallot (n=73)			
Isolated	15	25	14
TOF/PA	2	4	3
TOF/APV	4	2	0
TOF/CAVC	2	0	2
Repair of CAVC (n=45)	17	15	13
Arterial switch operation (n=37)			
TGA/IVS	5	7	8
TGA/VSD	3	4	5
TGA/IVS with coarctation repair*	0	2	0
TGA/VSD with coarctation repair*	2	0	1
Repair of ventricular septal defect (n=17)			
With interrupted aortic arch repair	3	2	1
With coarctation repair*	3	5	3
Mitral valve surgery (n=13)			
Valvuloplasty	4	3	3
Replacement	3	0	0
Repair of DORV (n=13)	5	4	4
Repair of TAPVR (n=12)	1	4	7
Repair of truncus arteriosus (n=11)	5	1	5
Ross procedure (n=6)			
Isolated	1	0	2
With Konno procedure	0	1	2
CPB support, min			
DHCA (n=57)	24.1±22.2	28.9±19.2	25.4±15.9
Cross-clamp time	76.3±36.5	70.1±30.9	77.8±29.7
CPB time	132.0±50.6	122.9±56.3	124.0±46.6
Total support time	136.5±52.1	130.5±54.2	131.6±48.3
Baseline inotropic score, μg/kg per min†	4.8	4.3	4.4

There were no significant differences among all variables by treatment group. Total support time was the sum of minutes of deep hypothermic circulatory arrest (if used) and cardiopulmonary bypass. Continuous variables are expressed as mean±SD.

APV indicates absent pulmonary valve; CAVC, complete atrioventricular canal; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; DORV, double outlet right ventricle; IVS, intact ventricular septum; PA, pulmonary atresia; TAPVR, total anomalous pulmonary venous return; and VSD, ventricular septal defect.

*Including arch augmentation.

†Geometric mean was used for baseline inotropic score (see text).

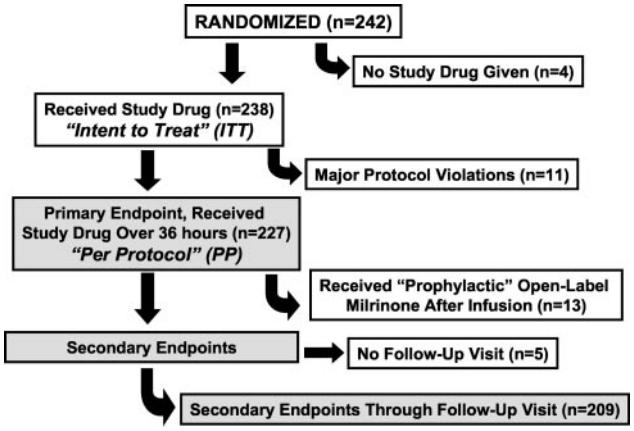

Figure 1. Flow diagram of patient evaluation in the PRIMACORP trial.

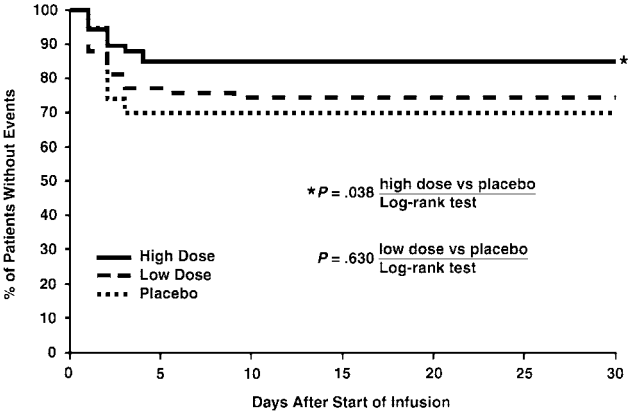

Figure 3. Time to development of LCOS/death through final visit. Six additional patients developed LCOS after discontinuation of study drug infusion.

metabolic acidosis.[13] The management of LCOS included the initiation of a new inotropic agent in 84.1%, escalation of existing pharmacological support (by at least 100% over baseline) in 43.2%, and initiation of extracorporeal membrane oxygenation in 4.5%.

The mean (geometric) duration of mechanical ventilation was similar in all 3 treatment groups (placebo, 1.6 days; low dose, 1.7 days; high dose, 1.7 days; $P=0.964$), as was the duration of hospital stay (placebo, 10.2 days; low dose, 8.6 days; high dose, 9.3 days; $P=0.159$). The percentage of patients who had a prolonged hospital stay (>15 days) was 23.3% in the placebo group, compared with 8.2% in the low-dose and 13.5% in the high-dose groups ($P=0.038$)

In both milrinone treatment arms, systolic (Figure 4) and diastolic blood pressures decreased between 5% and 9% immediately after the bolus and were not significantly different from placebo by 12 hours into the study infusion. Heart rate was significantly higher (mean, 10 bpm) in the treatment arms at 1, 12, and 24 hours compared with placebo. In the 117 patients with measured left atrial pressures, only the high-dose milrinone group experienced a significantly lower left atrial pressure compared with placebo; this occurred at the end of the bolus (7.7 versus 9.4 mm Hg, respectively). Right atrial pressures were measured in 208 patients, and there were no significant differences by treatment arm.

The mean urine output was 2.6 mL/kg per hour in the placebo group, 2.9 mL/kg per hour in the low-dose group, and 2.7 mL/kg per hour in the high-dose group. Creatinine clearance (mL/min per 1.73 m^2) was not different between groups (63.7 in placebo, 66.4 in low dose, and 62.4 in high dose), but was significantly less in neonates (mean, 37.2) compared with infants aged 1.0 to 4.8 months (mean, 59.2) and older children aged 4.8 months through 6 years (mean, 84.5). Serum lactate values were available at baseline in 224 of 238 patients, whereas mixed venous oxygen saturations were more variably measured at the study sites (only 141 patients at baseline). Because these values were not measured consistently at all sites and with a decreasing frequency during the study infusion, only limited conclusions can be drawn from these data. Consistent with previous studies,[2–5,15] the lowest mixed venous oxygen saturations and highest lactate values occurred in the first 12 hours after surgery. Although no statistically significant differences were identified between treatment groups, there was a trend toward a wider difference between arterial and mixed venous oxygen saturations at 8 and 12 hours after surgery in the placebo arm compared with those treated with high-dose milrinone (Figure 5, $P<0.07$).

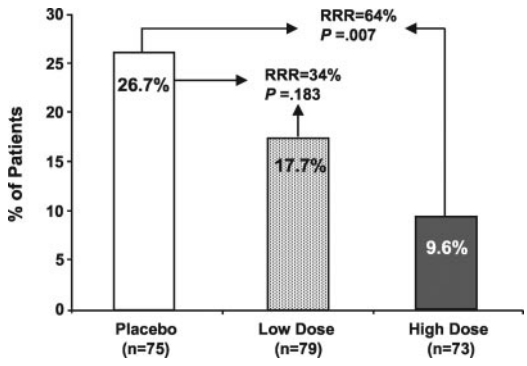

Figure 2. Primary end point: development of LCOS/death in the first 36 hours (per-protocol population, n=227).

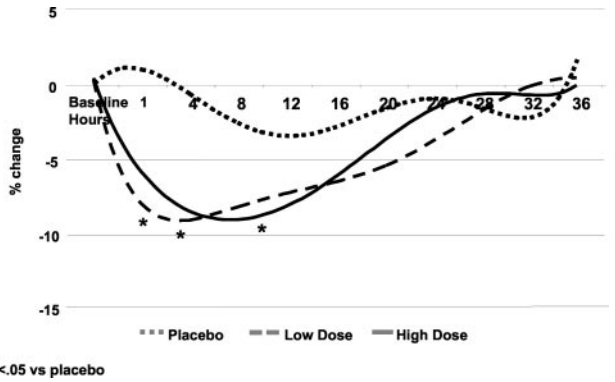

Figure 4. Percentage change from baseline in systolic blood pressure. The systolic blood pressure reductions were statistically significant from placebo in both the low- and high-dose arms at 1, 4, and 8 hours after the initiation of study drug. Similarly, the diastolic pressure reductions were statistically lower than placebo in both milrinone treatment arms at 1 and 4 hours (data not shown).

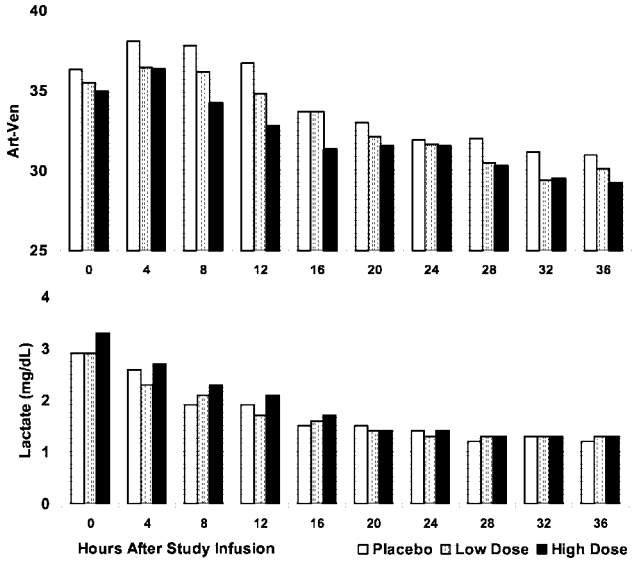

Figure 5. Difference between arterial and mixed venous oxygen saturations (Art-Ven; top) and serum lactate values (bottom) in the first 36 hours after surgery. There was a statistically insignificant trend ($P<0.07$) toward a wider Art-Ven difference in the placebo arm compared with those treated with high-dose milrinone at 8 and 12 hours after surgery.

Safety Analysis

The incidence of serious adverse events overall and by organ system was not significantly different among the treatment groups. Serial measurements showed no statistical difference in platelet count over time (baseline, 36 hours, 72 hours, and discharge) by treatment arm, and there was no difference in the incidence of thrombocytopenia (platelet count <50 000) during the study infusion (7.4% placebo, 8.8% low dose, and 2.6% high dose). Ventricular arrhythmia (n=1) and supraventricular tachycardia (n=1) were rare. Hypotension was reported in 1 patient in the placebo (1.2%) and low-dose (1.3%) arms and in 2 patients (2.6%) in the high-dose arm.

A secondary analysis was performed comparing patients who developed LCOS with those who did not. Those with LCOS had a significantly longer duration of mechanical ventilation (3.1 versus 1.4 days, $P=0.001$) and hospital stay (11.3 versus 8.9 days, $P=0.016$). Although urine output was significantly lower in those who developed LCOS (1.9 versus 2.5 mL/kg per hour, $P=0.002$) compared with those that did not, the 36-hour creatinine clearance was not significantly different. Compared with patients without LCOS, patients with LCOS had a wider difference between arterial and mixed venous oxygen saturations, as well as higher lactate levels (Figure 6).

Discussion

This study represents the largest randomized trial in a pediatric cardiac surgical population reported in the literature to date. The results of this study show a 64% relative risk reduction (patients with no major protocol violations) in the development of LCOS with the prophylactic use of high-dose milrinone. There was a statistically insignificant trend in patients treated with low-dose milrinone. The safety profile assessment showed no significant differences in the incidence of adverse events (eg, hypotension, arrhythmia, and thrombocytopenia) with either dose of milrinone compared with that of placebo.

In the present study, the diagnosis of LCOS was based on clinical experience and subjective findings and was adjudicated by a blinded end point committee. The 25.9% incidence of clinical LCOS in the placebo group of this trial is similar to that shown in other studies,[1,2,4] in which direct measurements of cardiac output were performed, where ≈25% of the patients had a cardiac index that was <2.0 L/min per m^2. As in previous studies,[2–4] most cases of LCOS occurred within

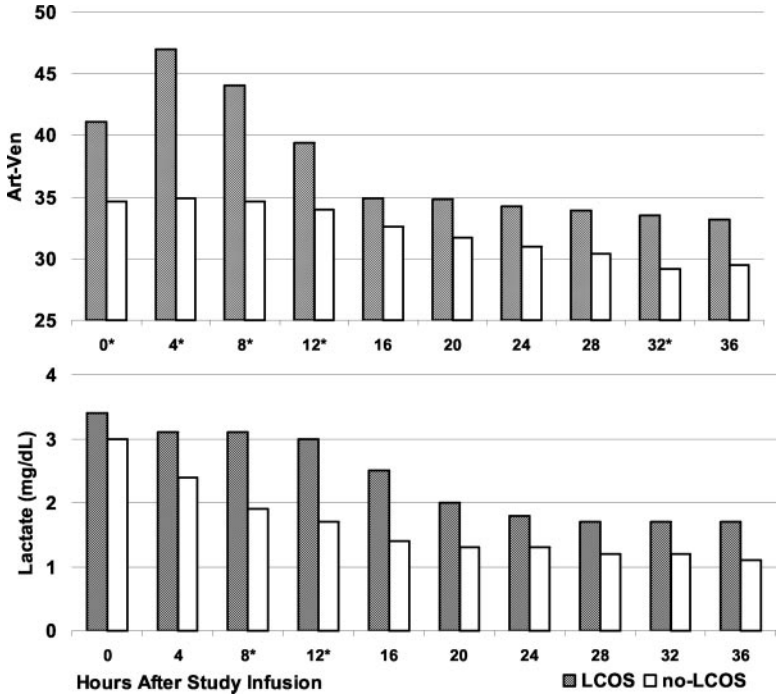

Figure 6. Difference between arterial and mixed venous oxygen saturations (Art-Ven; top) and serum lactate values (bottom) in the first 36 hours after surgery. Compared with patients without LCOS, those with LCOS had lower mixed venous oxygen saturations and higher lactate values throughout the study period; statistically significant differences ($P<0.05$) are marked with an asterisk.

the first 48 hours of surgery, typically in the first 12 to 18 hours (Figure 3). The beneficial result of preventing LCOS from surgery through the follow-up visit is almost certainly related to the effects seen in the immediate postoperative period rather than a prolonged effect on cardiac output.

In previous studies, milrinone has been shown to improve hemodynamics in pediatric patients with already established LCOS. In one study by Chang et al,[8] 10 neonates, age 3 to 27 days, with a mean cardiac index of 2.1 L/min per m^2 were given milrinone as a 50-μg/kg bolus followed by an infusion of 0.5 μg/kg per min. Compared with the hemodynamics at baseline, patients had significant increases in cardiac index and right and left ventricular stroke work index and significant decreases in right and left atrial pressures, mean systemic arterial pressure, pulmonary arterial pressure, and systemic and pulmonary vascular resistances.[8] These effects of milrinone were evident after the bolus and were maintained during the infusion. Similarly, Bailey et al[9] reported an 18% mean increase in the cardiac index in 20 patients with an age range of 3 to 22 months who received milrinone after cardiac surgery. Similar hemodynamic effects of milrinone have been observed in adults.[6,10]

The development of LCOS had a detrimental effect on the postoperative course, resulting in significantly lower urine output and a prolonged period of mechanical ventilation and hospital stay. Preventing morbidity related to LCOS may thus have a significant positive impact on recovery after surgery, which may result in important logistic, neurodevelopmental, and financial advantages in this high-risk pediatric population.

Although ventricular and supraventricular arrhythmias have been reported with the use of milrinone in adults, the use of low- or high-dose milrinone in pediatric patients was not associated with an increased risk of arrhythmia of either type. Similarly, hypotension occurred infrequently in this study, with no difference in the incidence among treatment groups. Finally, thrombocytopenia has been reported in adults and children who received milrinone after cardiac surgery. This study demonstrated no increased risk of thrombocytopenia in patients receiving milrinone. There were no differences by organ system among treatment groups in the incidence of adverse events.

Study Limitations

Objective assessments of cardiac output, such as thermodilution measurements of cardiac index, were not performed. A variety of problems (eg, residual cardiac lesions) make measurement of cardiac output more difficult in pediatric than adult patients. However, the primary end point did not simply involve a clinical diagnosis of LCOS; the end point was considered reached only if the practitioner felt that the patient warranted a significant escalation of support, such as a doubling of baseline support or adding a new pharmacological therapy. The study was not designed nor powered to determine a statistically significant difference in the laboratory parameters associated with LCOS nor the duration of hospital stay or mechanical ventilation. However, the trends were directionally consistent with the reduction in LCOS (Figure 5). In addition, the laboratory parameters in the LCOS group, such as an elevated serum lactate and lower mixed venous oxygen saturation, were additional supportive evidence of low cardiac output (Figure 6).

An additional limitation is that the study was limited to patients undergoing biventricular repair. Patients with other high-risk diagnoses and surgical procedures were not included, such as those undergoing staged reconstruction for forms of univentricular heart. Furthermore, some potentially eligible patients received milrinone in the operating room presumably to treat LCOS immediately after cardiac surgery. Hence, potentially highest risk patients were not included. Finally, although investigators were blinded to the study drug, the predictable hemodynamic changes during the institution of milrinone may potentially have resulted in bias. However, the hemodynamic changes seen in the first 24 hours, although statistically significant, were clinically small, and an independent committee adjudicated the primary end point in all cases.

Conclusion

The prophylactic use of high-dose milrinone (75-μg/kg bolus followed by a 0.75-μg/kg per min infusion) reduced the risk of LCOS after pediatric congenital heart surgery. Although hypotension, thrombocytopenia, and arrhythmias have been reported in adult patients, they occurred infrequently in pediatric patients and were not associated with milrinone use. We believe that strategies to prevent LCOS will result in shorter periods of hospitalization and fewer postoperative complications after pediatric congenital heart surgery.

Appendix

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References

1. Parr GVS, Blackstone EH, Kirklin JW. Cardiac performance and mortality early after intracardiac surgery in infants and young children. *Circulation*. 1975;51:867–874.
2. Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*. 1995;92:2226–2235.
3. Pesonen EJ, Peltola KI, Korpela RE, et al. Delayed impairment of cerebral oxygenation after deep hypothermic circulatory arrest in children. *Ann Thorac Surg*. 1999;67:1765–1770.
4. du Plessis AJ, Jonas RA, Wypij D, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. *J Thorac Cardiovasc Surg*. 1997;114:991–1000.
5. Nagashima M, Imai Y, Seo K, et al. Effect of hemofiltrated whole blood pump priming on hemodynamics and respiratory function after the arterial switch operation in neonates. *Ann Thorac Surg*. 2001;70:1901–1906.
6. Wright EM, Skoyles J, Sherry KM. Milrinone in the treatment of low output states following cardiac surgery. *Eur J Anaesthesiol*. 1992;9(suppl 5):21–26.
7. Ramamoorthy C, Anderson GD, Williams GD, et al. Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg*. 1998;86:283–289.
8. Chang AC, Atz AM, Wernovsky G, et al. Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med*. 1995;23:1907–1914.
9. Bailey JM, Miller BE, Lu W, et al. The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. *Anesthesiology*. 1999;90:1012–1018.
10. Feneck RO. Intravenous milrinone following cardiac surgery, I: effects of bolus infusion followed by variable dose maintenance infusion. The European Milrinone Multicentre Trial Group. *J Cardiothorac Vasc Anesth*. 1992;6:554–562.
11. Lang P, Wessel DL, Wernovsky G, et al. Hemodynamic effects of amrinone in infants after cardiac surgery. In: Crupi G, Parenzan L, Anderson RH, eds. *Perspectives in Pediatric Cardiology: Vol 2, Pediatric Cardiac Surgery, Part 2*. Mount Kisco: Futura Publishing; 1989:292–295.
12. Kikura M, Sato S. The efficacy of preemptive Milrinone or Amrinone therapy in patients undergoing coronary artery bypass grafting. *Anesth Analg*. 2002;94:22–30.
13. Hoffman TM, Wernovsky G, Atz AM, et al. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. *Am Heart J*. 2002;143:15–21.
14. Kulik TJ, Moler FW, Palmisano JM, et al. Outcome-associated factors in pediatric patients treated with extracorporeal membrane oxygenator after cardiac surgery. *Circulation*. 1996;94:II-63–II-68.
15. Charpie JR, Kekeon MK, Goldberg CS, et al. Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg*. 2000;120:73–80.