Prevention of Low Cardiac Output Syndrome After Pediatric Cardiac Surgery: A Double-Blind Randomized Clinical Pilot Study Comparing Dobutamine and Milrinone

Anna Cavigelli-Brunner, MD[1,2]; Maja I. Hug, MD[2,3]; Hitendu Dave, MD[2,4]; Oskar Baenziger, MD[2,3]; Christoph Buerki, MD[2,5]; Dominique Bettex, MD[6]; Vincenzo Cannizzaro, MD, PhD[2,3]; Christian Balmer, MD[1,2]

Objectives: Dobutamine and milrinone are commonly used after open-heart surgery to prevent or treat low cardiac output syndrome. We sought to compare efficacy and safety of these drugs in pediatric patients.

Design: Prospective, single-center, double-blinded, randomized clinical pilot study.

Setting: Tertiary-care university children's hospital postoperative pediatric cardiac ICU.

Patients: After written consent, 50 consecutive patients (age, 0.2–14.2 yr; median, 1.2 yr) undergoing open-heart surgery for congenital malformations were included.

Interventions: After cardiopulmonary bypass, a continuous infusion of either dobutamine or milrinone was administered for the first 36 postoperative hours. Maximum dose: dobutamine 6 µg/kg/min, milrinone 0.75 µg/kg/min.

Measurements and Main Results: There were no significant differences in demographic data, complexity of surgery, and intraoperative characteristics between the two study groups (dobutamine vs milrinone). Efficacy was defined as need for additional vasoactive support, which did not differ between groups (dobutamine 61% vs milrinone 67%; $p = 0.71$). Sodium nitroprusside was used more often in the dobutamine group (42% vs 13%; $p = 0.019$). Systolic blood pressure showed a trend toward higher values in the dobutamine group, whereas both drugs increased heart rate early postoperatively. Echocardiography demonstrated a consistently good cardiac function in both groups. Central venous oxygen saturation, serum lactate levels, urine output, time to chest tube removal, length of mechanical ventilation, ICU, and hospital stay were similar in both groups. Both drugs were well tolerated, no serious adverse events occurred.

Conclusions: Dobutamine and milrinone are safe, well tolerated, and equally effective in prevention of low cardiac output syndrome after pediatric cardiac surgery. The hemodynamic response of the two drugs is comparable. In uncomplicated cases, a trend toward the more cost-saving dobutamine might be anticipated; however, milrinone demonstrated a trend toward higher efficacy in afterload reduction. (*Pediatr Crit Care Med* 2018; XX:00–00)

Key Words: congenital heart disease; dobutamine; low cardiac output; milrinone; pediatric cardiac surgery; postoperative cardiac intensive care

[1]Department of Paediatric Cardiology, University Children's Hospital Zurich, Zurich, Switzerland.

[2]Children's Research Centre, University Children's Hospital Zurich, Zurich, Switzerland.

[3]Department of Intensive Care Medicine and Neonatology, University Children's Hospital Zurich, Zurich, Switzerland,

[4]Department of Congenital Cardiovascular Surgery, University Children's Hospital Zurich, Zurich, Switzerland.

[5]Department of Anaesthesia, University Children's Hospital Zurich, Zurich, Switzerland.

[6]Department of Anaesthesiology, University Hospital Zurich, Zurich, Switzerland.

Supported, in part, by a private donation.

Dr. Balmer received grant support funding from a private donation (the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article). The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: anna.cavigelli@kispi.uzh.ch

DOI: 10.1097/PCC.0000000000001533

Low cardiac output syndrome (LCOS) is frequent in infants and children after surgery for congenital heart defects and occurs typically 6–18 hours post surgery (1). It postpones recovery and contributes to morbidity and mortality (1, 2). IV inotropic agents and vasodilators are routinely used in the postoperative care for prevention and/or therapy of a LCOS (2–5).

Dobutamine is a synthetic direct-acting β1- and β2-adrenergic receptor agonist with positive inotropic and mild

chronotropic effects (6). Furthermore, it induces mild vasodilation of the pulmonary and systemic vascular bed (7, 8). It has a rapid onset of action, a short half-life and its infusion rate is positively correlated to plasma concentrations (9). Dobutamine is used in clinical practice since 1975, and its pharmacokinetics have been studied in children (9, 10).

Milrinone is a selective inhibitor of the type III phosphodiesterase. It acts as a positive inotropic agent, reduces systemic and pulmonary vascular resistance, and enhances lusitropy with minimal increase in myocardial oxygen consumption (3, 7, 11–13). Milrinone is used in clinical practice since the early 1990s (7), and it is nowadays the most frequently used drug to prevent postoperative LCOS in children after cardiac surgery in Europe (5). In the postoperative care of children and neonates after open-heart surgery, milrinone has proved to be safe and shows an acute beneficial effect on hemodynamics: it improves cardiac index, decreases filling pressures, and decreases pulmonary vascular resistance (3, 13). It has also been shown that milrinone reduces the relative risk of a postoperative LCOS by as much as 64% (Primacorp [2]) and that there is a beneficial effect in optimization of cardiovascular function in the acute setting in the pediatric age group (14).

In adults, dobutamine and milrinone resulted in a similar significant and sustained increase in cardiac index, and both drugs were effective in improving the general hemodynamic variables in postsurgical cardiac patients (6, 15).

In our institution as well as in other European institutions (5), milrinone is the drug of first choice for prevention and therapy of postoperative LCOS in the pediatric age group. However, some institutions prefer among others the considerably less expensive dobutamine for the same indication. Overall, there is marked variability in various preventive drug therapies, with only sparse evidence available, and the decision to use one or the other drug is mostly based purely on institutional preference (5).

Our hypothesis is that dobutamine and milrinone are equal for the prevention of a postoperative LCOS. With this study, we compared efficacy and side effects of dobutamine and milrinone in children during the first postoperative period after open-heart surgery.

METHODS

Study Design and Population

We conducted a single-center, prospective, double-blinded, randomized trial with patients undergoing cardiac surgery for congenital heart defects at the University Children's Hospital Zurich, Switzerland. Written informed consent was obtained. The study was approved by the local ethical committee.

All infants and children older than 6 weeks of age undergoing cardiac surgery on cardiopulmonary bypass (CPB) with a risk of postoperative LCOS based on the intracardiac anatomy and the performed surgery and in whom routine administration of postoperative inotropic support was anticipated were included into the study.

Patients with a body weight below 3 kg or above 35 kg, with significant postoperative left ventricular outflow tract obstruction or the need of extracorporeal membrane oxygenation, were excluded from the study.

Interventions

Patients were randomized into two groups receiving an infusion of either dobutamine (Dobutrex; Teva Pharma AG, Basel, Switzerland) or milrinone (Corotrop; Sanofi-Aventis SA, Vernier, Switzerland) for the first 36 hours postoperatively in a blinded fashion. The anesthetist started the study drug with an IV bolus of 50 µg/kg (maximum 1 mg) milrinone or sodium chloride 0.9%, respectively, over 15 minutes. Then, a continuous infusion (1 mL/hr) of the study drug was started. Upon arrival in the ICU, the continuous infusion was gradually increased to 2 mL/hr at 4 hours post arrival on ICU resulting in a target dose of 6 µg/kg/min dobutamine and 0.75 µg/kg/min milrinone, respectively, which remained unchanged until 24 hours after arrival on ICU. Any other drug, for example, adrenaline, noradrenaline, or sodium nitroprusside, could be added to the study drug if indicated. The decision to initiate an additional drug was taken by the attending intensivist according to his/her individual clinical judgement and a combination of variables describing a LCOS (blood pressure lower than the age-related normal values, central venous oxygen saturation [$Scvo_2$] value < 30% of the arterial saturation, diuresis < 1 mL/kg/hr, peripheral temperature < 32°C, serum lactate > 3 mmol/L). After 24 hours, the study drug was tapered down to 1.5 mL/hr, at 30 hours to 1 mL/hr, and at 36 hours it was stopped. In patients with persisting heart failure, a new continuous infusion of milrinone was started in a nonblinded fashion.

Objectives

To analyze the efficacy of the study medications, we determined as primary endpoint the occurrence of LCOS in each study group. As measurement, we chose the additional amount of vasoactive support within the first 48 hours postoperatively. This was assessed by comparing the number of patients who needed supplementary vasoactive support (adrenaline, noradrenaline, or sodium nitroprusside) in addition to the standardized application of the study drugs dobutamine or milrinone. Dobutamine and milrinone were not allowed as additional drugs during the continuous infusion of the study drug.

As secondary outcomes, the following variables were assessed: blood pressure; heart rate; diuresis; respiratory rate; Fio_2; peripheral circulation (capillary refill time, peripheral temperature); central to peripheral temperature gradient; central venous So_2 and serum lactate; myocardial fractional shortening and ejection fraction at repeated echocardiographic evaluations; total duration of mechanical ventilation, inotropic support, and chest drainages; and length of ICU and hospital stay. The occurrence of adverse events was registered, and deaths were assessed up to 28 days

Randomization

The randomization was stratified by weight to ensure a balance across the study groups. (group I: 3–10 kg, group II: > 10 to 24 kg, group III: > 24 to 35 kg).

Eligible patients were randomly assigned to study groups in a 1:1 ratio (dobutamine and milrinone groups). Stratified randomization was accomplished using the minimization approach with biased coin assignment. Investigators, staff, and participants were blinded to the assigned group until after the end of the study.

Study Procedures and Data Collection

All invasive and noninvasive procedures were part of the standard treatment plan of our hospital. Hemodynamic monitoring consisted of central venous and peripheral arterial catheter for continuous invasive pressure monitoring in all patients. Skin and rectal temperatures were measured continuously. Heart rate was constantly monitored with a five-leads electrocardiogram (ECG) and blood oxygen saturation with a continuous pulse oximeter. All patients were postoperatively mechanically ventilated with ventilation and weaning strategies according to the institutional standards. The central venous So_2 was obtained from central venous catheter, pH, arterial So_2, Pao_2, $Paco_2$, base excess, lactate levels, hemoglobin, electrolytes, glucose, creatinine, troponin, creatine kinase, and creatinine kinase-MB from the arterial catheter. Pericardial, mediastinal, and pleural chest drains were each removed when draining less than 0.5 mL/kg/hr. Urine output was recorded.

Data collection of invasive and noninvasive monitoring and ventilation was performed at arrival on ICU (time = 0) and every 4 hours thereafter for 48 hours. Blood tests were recorded every 8 hours. Echocardiography and 12-leads ECG were performed prior to the operation and three times afterwards: at 2–6, 24–30, and 48–54 hours after arrival on the ICU.

Statistic Analysis

Data are presented as frequencies, mean ± SD, or median and range as appropriate. Qualitative data are expressed as absolute numbers and percentage. Statistical significance is defined by p values of less than 0.05. For the primary endpoint, categorical variables are described as numbers (n) and percentages, then the two groups were compared using the chi-square test.

Secondary endpoints were visually examined for extreme observations and were analyzed by comparing the trend of each variable over the first postoperative 48 hours using various graphs and student t tests where appropriate.

Single ventricle patients were compared with patients without single ventricles in their age group with the Mann-Whitney U test.

Since this study was designed as a pilot study, no power calculation was performed.

All calculations were done using SPSS for Windows XP version 22 (SPSS 22.0.0.0; IBM Corp., Armonk, NY)

RESULTS

A total of 96 patients were assessed for eligibility. Fifty individuals were eventually enrolled and randomized, 26 were allocated to the dobutamine, and 24 to the milrinone group.

The median age of the analyzed patients was 1.2 years (0.2–14.2 yr), the median weight 8.6 kg (3.4–35.5 kg). Enrollment

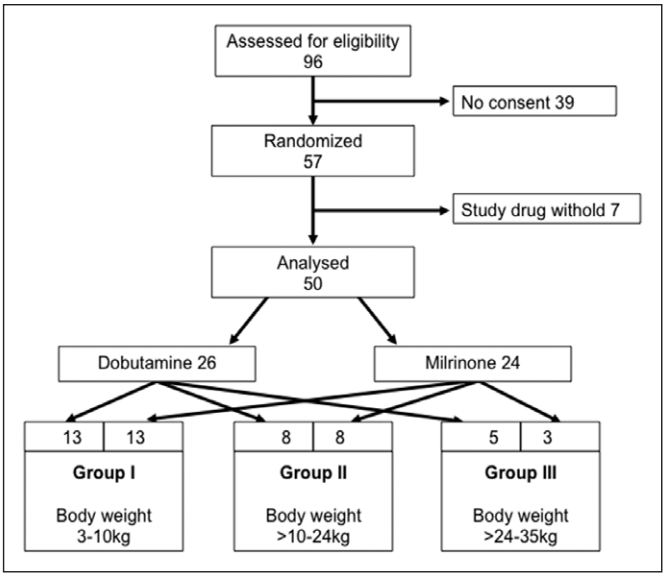

Figure 1. Flow chart of enrollment. Numbers indicate number of patients in each group

characteristics and distribution of patients into subgroups are shown in **Figure 1**. Infants belonging to subgroup I were represented with 26 patients (52%). There were no differences between the two study groups (dobutamine vs milrinone) in demographic data, complexity of surgery, and intraoperative characteristics (**Table 1**). In subgroup II, four children had single ventricles: three of the milrinone and one of the dobutamine group.

The need for additional vasoactive support due to the occurrence of a LCOS within the first 48 hours postoperatively, which was the primary objective of the study, did not differ between the two study groups, nor between the subgroups. It affected 16 patients of each group (61% in the dobutamine vs 67% in the milrinone group; $p = 0.71$). The duration of additional vasoactive support was also equal in the two groups (30 ± 20 vs 28 ± 22 hr; $p = 0.37$), also independently of the body weight. In the dobutamine group, significantly more patients needed additional afterload reduction with sodium nitroprusside: 11 patients (42%) versus three patients (13%), p value equal to 0.019. None of the patients with single ventricle needed sodium nitroprusside. The remaining vasoactiva were distributed as follows (some patients needed > one additional drug): adrenaline was necessary in six patients of the dobutamine and in nine of the milrinone group, noradrenaline in three of the dobutamine and five of the milrinone, and after completing the study drug, milrinone was started in three patients of each group.

There was no difference between the two groups (dobutamine vs milrinone) in length of mechanical ventilation: 7 hours (0–50 hr) versus 8 hours (1–78 hr), p value equal to 0.069, length of ICU stay: 2 days (2–10 d) versus 3 days (2–7 d), p value equal to 0.55, and length of hospital stay: 10 days (7–69 d) versus 14 days (8–78 d), p value equal to 0.18. Comparing the subgroups, time to extubation was significantly shorter in the dobutamine group I (patients ≤ 10 kg) compared with that in the corresponding milrinone group: median 19.2 hours (11.3–22.9 hr) versus 32.5 hours (19.8–56.3 hr), p value equal to 0.03.

TABLE 1. Demographic Data, Operation Characteristics, and Observed Arrhythmias

Study Population	Dobutamine	Milrinone
n	26	24
Demographics		
Male, *n* (%)	13 (50)	15 (63)
Age at surgery (yr), median (minimum to maximum)	1.7 (0.2–14.2)	0.7 (0.2–11)
Weight at surgery (kg), median (minimum to maximum)	10.4 (3.8–35)	6.9 (3.4–27.7)
Down's syndrome, *n*	7	6
Other syndromes, *n*	2	3
Surgical procedure, *n*		
Ventricular septal defect or atrioventricular septal defect closure	13	11
Left ventricular outflow tract repair	4	3
Right ventricular outflow tract repair	4	2
Tetralogy of Fallot repair	2	2
Fontan completion with extracardiac conduit	1	2
Pulmonary vein stenosis repair	1	1
Unifocalization pulmonary arteries in single ventricle		1
Aortopulmonary window repair		1
Mitral valve replacement		1
Anomalous origin of the right coronary artery repair	1	
Perioperative characteristics, median (minimum to maximum)		
Cardiopulmonary bypass time (min)	126 (73–345)	141 (66–337)
Aortic cross clamp time (min)	68 (0–143)	63 (0–166)
Adverse events: arrhythmia (total), *n*	4	7
AVB III	1	
Persistent, requiring permanent pacemaker		
Transient		3
AVB II type Wenckebach	1	1
Junctional ectopic tachycardia	1	1
Supraventricular tachycardia	1	1
Atrial ectopic tachycardia		1

AVB = atrioventricular block.

Overall, there was no clinically significant difference in all measured hemodynamic variables between the two study groups. Furthermore, no significant difference was found in mean arterial blood pressures since dobutamine produced a trend toward higher systolic, whereas the milrinone group showed a nonsignificant increase of diastolic blood pressure (**Figs. 2** and **3**). Dobutamine as well as milrinone increased heart rate similarly in the first postoperative hours (**Fig. 4**). Last, we observed no significant difference in central venous So_2 and lactate levels.

The time to chest tube removal was equal in both groups. Ventricular function as measured by repeated transthoracic echocardiography was within the normal limits in all patients with no difference between the two study groups.

The hemodynamic variables of the four patients with single ventricles did not differ significantly from those of patients with biventricular repair within the same weight group.

Both drugs were well tolerated, and no serious adverse events occurred. No hospital or additional deaths occurred during follow-up. In one patient in the dobutamine group, renal failure requiring temporary hemodialysis occurred postoperatively. The occurrence of a low platelet count was similar in both groups. Arrhythmias were observed in both groups with no preference to either group (Table 1).

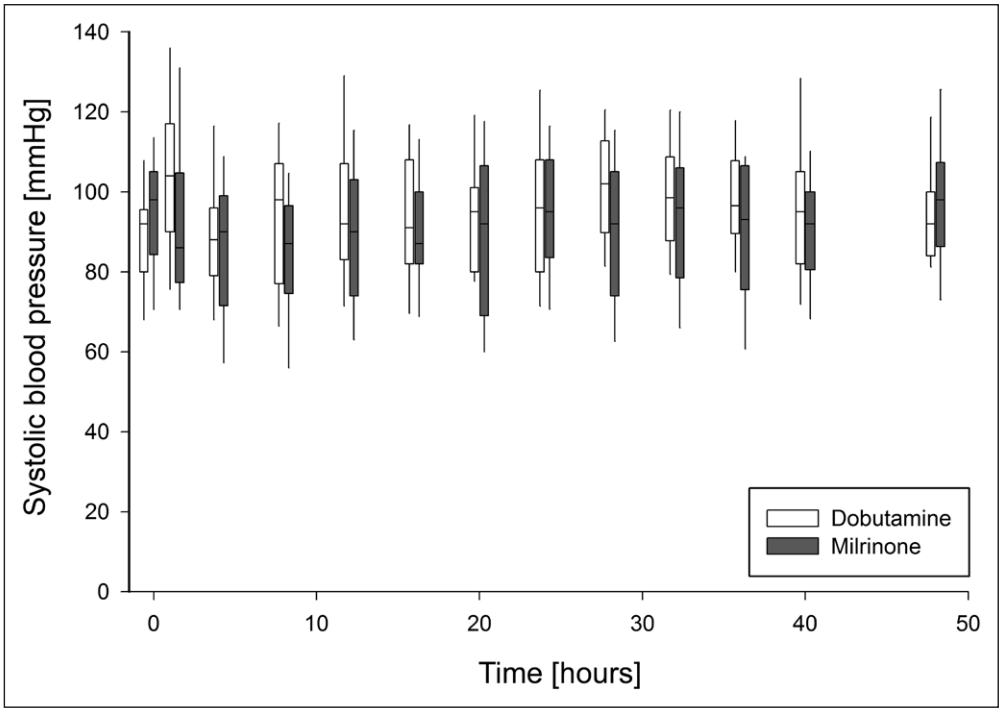

Figure 2. Systolic blood pressure during the first 48 hr postoperatively. *Boxes* represent median and 25–75th percentile; *whiskers* represent minimum and maximum.

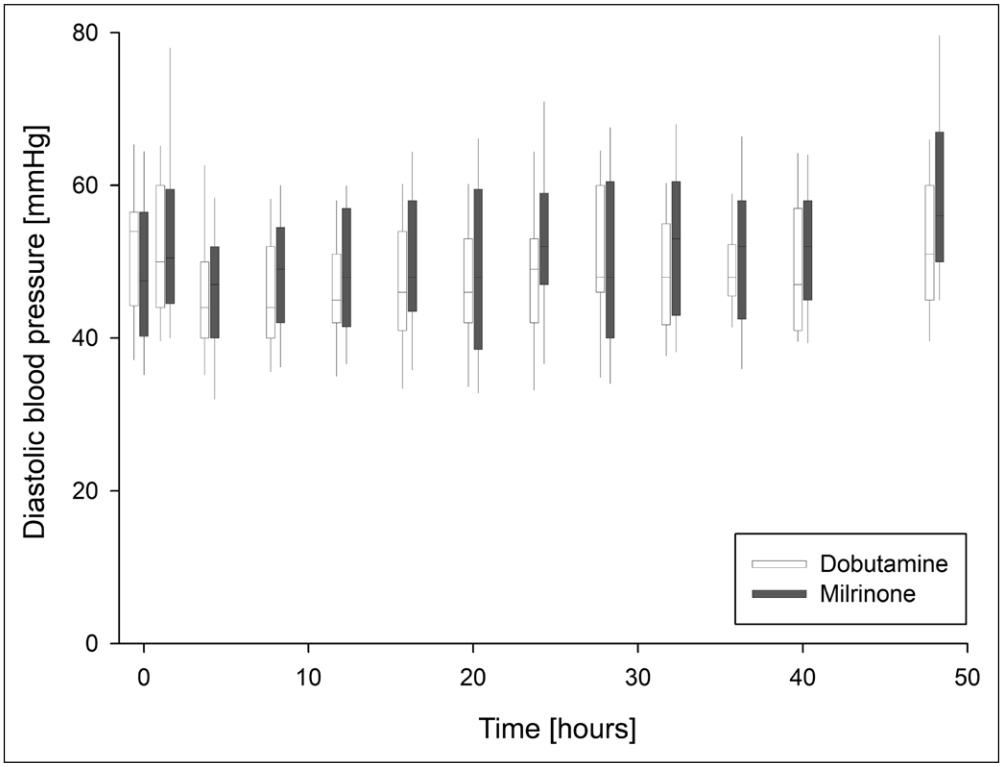

Figure 3. Diastolic blood pressure during the first 48 hr postoperatively. *Boxes* represent median and 25–75th percentile; *whiskers* represent minimum and maximum.

DISCUSSION

To our knowledge, the present study is the first randomized double-blind trial comparing dobutamine and milrinone for the postoperative prevention or treatment of LCOS in pediatric patients after surgery for congenital heart defects. We were able to show that both drugs were effective and could be safely used in postoperative pediatric patients. This finding is in accordance with the results of a similar multicenter study in adults (6) and a retrospective analysis of adult heart failure patients (16).

The efficacy of the study drug was assessed by comparing the number of patients who needed supplementary vasoactive support in addition to the standardized application of the study drugs dobutamine or milrinone. Furthermore, we compared hemodynamic variables of LCOS within the first 48 postoperative hours.

There was no difference in the use of additional vasoactive support, which was necessary in 16 patients in each group; also, the hemodynamic response was similar in both study groups. Hence we conclude that both drugs (dobutamine and milrinone) are equally effective in the prevention of a LCOS in the postoperative period after surgery for pediatric congenital heart defects. Of note, additional application of sodium nitroprusside due to an increased blood pressure was used more often in the dobutamine group suggesting that milrinone promotes more systemic vasodilation than dobutamine with our dose regime.

Exactly the same effect has been described previously in two adult populations, which validates the findings in our pediatric population: in a retrospective analysis of 329 patients with advanced heart failure (16) and in a randomized open-label multicenter trial with 120 adults after cardiac surgery (6), dobutamine compared with milrinone was also associated with a higher occurrence rate of hypertensive blood pressure. However, the dobutamine doses used in the first study were two to three folds higher than ours, which may explain the excessive increase of blood pressure.

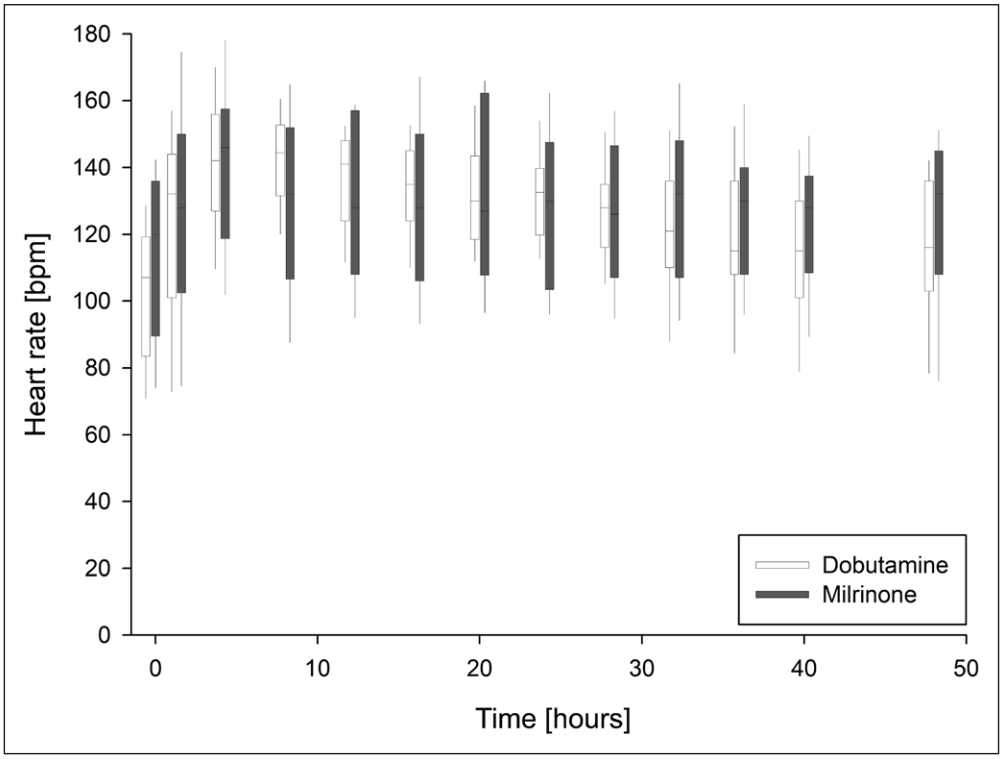

Figure 4. Heart rate during the first 48 hr postoperatively. *Boxes* represent median and 25–75th percentile; *whiskers* represent minimum and maximum.

We tried to conduct our study as close as possible to our daily routine and local conditions. The patient population and the present heart defects reflect the current spectrum in pediatric cardiology with predominantly septal defects in infants. Single ventricles constituted 8% of the total cohort (4/50). Interestingly, their postoperative performance did not differ from that of patients with biventricular repair of the same group, indicating that both dobutamine and milrinone are appropriate medications for this patient group in the management or prevention of postoperative LCOS. In a double-blinded randomized study in patients after Fontan completion, however, postoperative milrinone was not associated with improved early clinical outcome and had to be discontinued in a quarter of subjects due to hypotension (17). Even though we did not observe relevant hypotension or other adverse events in our study cohort, milrinone has to be used with caution in single ventricle patients, especially after Fontan completion.

In our study, clinical outcome and complication rates were similar in both groups (dobutamine and milrinone). No significant differences in the length of mechanical ventilation or the ICU stay were detected, and both groups did not have any in-hospital or late mortality. Interestingly in this context, there is no evidence however about a beneficial effect of milrinone on the long-term morbidity and mortality (14, 18).

Arrhythmia has been described as a side effect of dobutamine and milrinone. There is conflicting evidence about the extent of the arrhythmogenic effect of milrinone. A prospective observational study of 603 pediatric patients after cardiac surgery found that milrinone was independently associated with a nearly three-fold increase in the odds of a postoperative tachyarrhythmia prompting intervention (19). They concluded that milrinone is an independent risk factor for clinically significant tachyarrhythmias in the early postoperative period after congenital heart surgery. In patients after Fontan completion, arrhythmias were registered nearly twice as much in the milrinone group compared with the placebo group. In contrast, in the Primacorp trial, arrhythmias were rare and occurred with an incidence of only 0.8% (2). In our cohort, the overall incidence of arrhythmia was low and did not differ between the two study groups. The occurrence of arrhythmia seemed to be more related to the type of performed operation than to the currently applied medication.

Sinus tachycardia is often described as side effect of dobutamine due to its direct action on the β-adrenergic receptors and may be dose dependent (20). In our study, in both groups heart rates were slightly elevated during the whole study period. This might be due to agitation, pain or elevated body temperature, which are well-known trigger of an elevated heart rate in the postoperative setting. Furthermore CPB-triggered inflammation response or postoperative myocardial recovery might also provoke sinus tachycardia.

In our country, a postoperative support with milrinone is three to four times more costly than with dobutamine. This aspect has also to be taken into account when choosing a medication in a specific patient.

For practical reasons, the number of participants is relatively small, reducing the statistical power of our study. A further limitation is the heterogeneity of the study population with regard to their hemodynamics due to the large spectrum of congenital heart defects. A mix of diagnoses and operations is included, typically seen in pediatric congenital heart surgery; therefore, we assume the results are valid and interesting for most centers. However, a generalization should be done carefully. Furthermore, other drug dose regimes would possibly have resulted in different outcomes. For milrinone, we used the recommended efficacy dose (2), and for dobutamine, we used our house standard dose. The variability of the clinical judgment of the responsible intensivist at bedside is another possible confounder, which we tried to overcome with clearly defined thresholds for the diagnosis of LCOS in a way that reflects our current practice. But, it still remains a clear limitation of our study.

We measured and compared urine output, but we did not systematically assess fluid intake. Therefore, we cannot make a statement about a difference between the study groups in the amount of fluid needed to keep the circulation stable. Transfusion policy was similar in both groups; hence, we did not analyze the use of blood and blood components between the groups.

On purpose, we excluded patients younger than 6 weeks of age because of ethical reasons, even though this is a relevant and interesting population in pediatric congenital heart surgery.

CONCLUSIONS

In our study cohort, dobutamine and milrinone are equally effective, safe, and well tolerated for the prevention of a postoperative LCOS in pediatric patients after cardiovascular surgery. In uncomplicated cases, a trend toward the less expensive dobutamine might be anticipated, especially in patients who would benefit from a mild increase in blood pressure. In patients with the need of profound afterload reduction, milrinone may be advantageous. However, we acknowledge the limited power of our pilot trial. Hence, clinical implications have to be interpreted with caution. Also, postoperative vasoactive therapy has to be tailored individually and continuously adapted to the specific patient needs, frequently including more than one single medication. The knowledge gained from our pilot trial has the potential to contribute to the successful conduct of future larger scale studies.

ACKNOWLEDGMENTS

We thank Barbara Külling, Johanna Schelp, and Ghazala Gohar for their contribution in the collection and analysis of the data and Daniel Fetz for providing support for the randomization and preparing the study medication.

REFERENCES

1. 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
2. Hoffman TM, Wernovsky G, Atz AM, et al: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; 107:996–1002
3. 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
4. Wessel DL: Managing low cardiac output syndrome after congenital heart surgery. *Crit Care Med* 2001; 29(10 Suppl): S220–S230
5. Vogt W, Läer S: Prevention for pediatric low cardiac output syndrome: Results from the European survey EuLoCOS-Paed. *Paediatr Anaesth* 2011; 21:1176–1184
6. Feneck RO, Sherry KM, Withington PS, et al; European Milrinone Multicenter Trial Group: Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. *J Cardiothorac Vasc Anesth* 2001; 15:306–315
7. Francis GS, Bartos JA, Adatya S: Inotropes. *J Am Coll Cardiol* 2014; 63:2069–2078
8. Overgaard CB, Dzavík V: Inotropes and vasopressors: Review of physiology and clinical use in cardiovascular disease. *Circulation* 2008; 118:1047–1056
9. Mahoney L, Shah G, Crook D, et al: A literature review of the pharmacokinetics and pharmacodynamics of dobutamine in neonates. *Pediatr Cardiol* 2016; 37:14–23
10. Habib DM, Padbury JF, Anas NG, et al: Dobutamine pharmacokinetics and pharmacodynamics in pediatric intensive care patients. *Crit Care Med* 1992; 20:601–608
11. Garcia Guerra G, Joffe AR, Senthilselvan A, et al: Incidence of milrinone blood levels outside the therapeutic range and their relevance in children after cardiac surgery for congenital heart disease. *Intensive Care Med* 2013; 39:951–957
12. Bishara T, Seto WT, Trope A, et al: Use of milrinone in critically ill children. *Can J Hosp Pharm* 2010; 63:420–428
13. Bailey JM, Miller BE, Lu W, et al: The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. *Anesthesiology* 1999; 90:1012–1018
14. Meyer S, Gortner L, Brown K, et al: The role of milrinone in children with cardiovascular compromise: Review of the literature. *Wien Med Wochenschr* 2011; 161:184–191
15. Carmona MJ, Martins LM, Vane MF, et al: Comparison of the effects of dobutamine and milrinone on hemodynamic parameters and oxygen supply in patients undergoing cardiac surgery with low cardiac output after anesthetic induction. *Rev Bras Anestesiol* 2010; 60: 237–246
16. Yamani MH, Haji SA, Starling RC, et al: Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: Hemodynamic efficacy, clinical outcome, and economic impact. *Am Heart J* 2001; 142:998–1002
17. Costello JM, Dunbar-Masterson C, Allan CK, et al: Impact of empiric nesiritide or milrinone infusion on early postoperative recovery after Fontan surgery: A randomized, double-blind, placebo-controlled trial. *Circ Heart Fail* 2014; 7:596–604
18. Burkhardt BE, Rücker G, Stiller B: Prophylactic milrinone for the prevention of low cardiac output syndrome and mortality in children undergoing surgery for congenital heart disease. *Cochrane Database Syst Rev* 2015; 3:CD009515
19. Smith AH, Owen J, Borgman KY, et al: Relation of milrinone after surgery for congenital heart disease to significant postoperative tachyarrhythmias. *Am J Cardiol* 2011; 108:1620–1624
20. Romson JL, Leung JM, Bellows WH, et al: Effects of dobutamine on hemodynamics and left ventricular performance after cardiopulmonary bypass in cardiac surgical patients. *Anesthesiology* 1999; 91:1318–1328