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First experiences with intraoperative Levosimendan in pediatric cardiac surgery

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Abstract Levosimendan is a calcium-sensitizing agent with effective inotropic properties. It has been shown to improve cardiac function, hemodynamic performance, and survival in adults with severe heart failure. However, the effect of Levosimendan in pediatric cardiac surgery has not yet been investigated. Thus, we report on our experience with the intraoperative application of Levosimendan in seven infants (body weight range 2.6–6.3 kg) with severe myocardial dysfunction after complex congenital heart surgery. During the administration of Levosimendan, the heart rate, mean arterial blood pressure, and central venous pressure did not change. The mean arterial lactate level significantly decreased 24 and 48 h after the first infusion compared to baseline. Central venous oxygen saturation increased significantly 24 and 48 h after the onset of Levosimendan infusion. We found intraoperatively administered Levosimendan to be well tolerated in the seven infants with severe myocardial dysfunction after complex congenital heart surgery. Levosimendan is a new rescue drug which has beneficial effects, even in pediatric cardiac surgery.

Keywords Cardiac surgery · Congenital heart failure · Hemodynamic · Levosimendan · Central venous oxygen saturation · Lactate acid

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Introduction

Low cardiac output early after cardiopulmonary bypass (CPB) is a well known problem in the early postoperative course after complex congenital heart surgery that affects the postoperative recovery of about 25% of patients [5]. It may cause prolonged mechanical ventilation, increased risk of infection and sepsis, longer stay in the intensive care unit (ICU), and increased mortality [19]. Therefore, the early treatment or, better, the prevention of a low cardiac output state should be a major concern of the intraoperative and early postoperative management of these patients. Inotropes are effective drugs for the acute treatment of low cardiac output. However, they may have negative side effects, such as the increase of myocardial oxygen consumption, with the consequent risk of ischemia and arrhythmia. Furthermore, tachyphylaxia, desensitization of adrenergic pathways in patients with chronic heart failure, and the concomitant use of β-blockers may limit the efficacy of inotropes, particularly in those patients who are especially dependent on it [12]. Thus, therapeutic agents with a more specific mode of action would be particularly helpful in this group of patients.

The new therapeutic agent, Levosimendan, has been shown to improve cardiac function, hemodynamic performance, and survival in adults with severe heart failure [4, 9]. Levosimendan is a calcium-sensitizing agent which has

a relevant inotropic effect by sensitizing myocardial troponin C to calcium [3]. Additionally, Levosimendan is a vasodilator, stimulating adenosine triphosphate-dependent potassium channels of systemic, pulmonary, and coronary vascular smooth-muscle cells [2, 6, 7, 10]. All of these properties are, theoretically, useful after pediatric cardiac surgery, but, so far, there are only very few clinical reports on its application in children [1, 11]. Here, we describe our preliminary experience with Levosimendan for the therapy of severe myocardial dysfunction after complex congenital heart surgery in infants.

Methods

Patients

Seven of 194 consecutive pediatric patients undergoing surgery for congenital heart disease between October 2006 and December 2007 received Levosimendan and were included in this retrospective pilot study. Due to our strictly respected ICU protocol, data were collected comparable to a prospective study. We applied Levosimendan in patients who were at an elevated risk for low cardiac output, characterized by factors such as preoperatively impaired ventricular function, prolonged cross-clamp time, and an increased need of inotropes early after CPB. Our aim was to combine effective pharmaceutical circulatory support with prevention of the known adverse events of high catecholamine doses.

Informed consent included eventual pharmaceutical circulatory support without a special note on Levosimendan. According to the guidelines of the German **A**rbeitsgemeinschaft der **W**issenschaftlichen **M**edizinischen **F**achgesellschaften (Working Group of Scientific Medical Faculties), "Levosimendan may be used on a compassionate use basis in patients with acute severe symptomatic perioperative low cardiac output syndrome, caused by systolic dysfunction." Our patients were treated in an early state of this condition. If Levosimendan would not have been available, further support with inotrope substances would have been given. Depending on the hemodynamic response, either these measures could have been sufficient and well tolerated, or further support including mechanical devices such as an extracorporeal membrane oxygenation machine (ECMO) would have been necessary.

In four children, Levosimendan infusion was started while weaning from CPB. In the remaining three infants, the drug was administered after the termination of CPB, but before chest closure. All patients received Levosimendan (Simdax®, Orion Pharma, Espoo, Finland) at a loading dose of 12 µg kg^{-1} over 10 min, followed by a continuous infusion of 0.2 µg kg^{-1} min^{-1} for 24 h. In those patients in whom Levosimendan infusion was administered on CPB, hemodynamic parameters at the onset of Levosimendan infusion were not documented (because the patients were still on a pump). For comparison, hemodynamic parameters as well as lactate levels were documented during Levosimendan infusion at defined points of time as follows: at the onset of Levosimendan infusion and at 1, 3, 6, 12, 24, and 48 h post-infusion. Additionally, central venous oxygen saturation (ScvO$_2$), which has been shown to correlate well with cardiac output [14], was recorded. This parameter was routinely monitored in the operating room (OR) and in the ICU, respectively.

After prolonged bypass time and extended cardiosurgical interventions, we liberally utilize Milrinone (up to 1.0 µg kg^{-1} min^{-1}) and Ephedrine (up to 0.3 µg kg^{-1} min^{-1}) in order to keep the mean arterial pressure (MAP) above 50 mmHg. If necessary, nitrates are given to lower excessive peripheral resistance. Heart rates up to 200 bpm remain untreated; a careful elevation of serum potassium levels to 5 mEq/L is used as an early first-line treatment if this limit is exceeded. Moderately increased venous filling pressures up to central venous pressure (CVP) values of 14 to 16 mmHg support the systolic function via the Frank-Starling mechanism, but to avoid excessive peripheral edema, we try to return to normal values as soon as possible. The type of volume was predominantly crystalloid solution. Short ventilation times have lower priority than a well-controlled stabilization of the cardiac output and the circulation.

To achieve comparable ScvO$_2$ values in patients with a right-to-left shunt, i.e., impaired arterial saturation (SaO$_2$), we adjusted the ScvO$_2$ to a normal arterial saturation of 98% by using the following calculation: calc ScvO$_2$=98 − (SaO$_2$ − ScvO$_2$). This was necessary for both patients with mitral valve atresia and hypoplastic left heart syndrome. Factors influencing this calculation, such as lung/pulmonary edema, arterio-venous shunts, or septic shock, were nonexistent in the seven patients.

Statistical analysis

Data collection was based on anesthesiologic protocols and ICU charts. Hemodynamic data and catecholamine/inotropic support were expressed as mean ± standard deviation (SD); if the standard deviation was larger than the mean, we indicated the median and range. A paired *t*-test was used to compare the mean values of ScvO$_2$, lactate, MAP, CVP, heart rate, epinephrine, and milrinone infusion.

As four patients received Levosimendan during CPB, their hemodynamic parameters were not evaluable at time "0". A *p*-value of less than 0.05 was considered to be statistically significant. All data were analyzed using data analysis and graphing software (Origin™ version 5.0, Microcal, Northampton, USA).

Table 1 Patient characteristics

Patient no.	Age, days	Diagnosis, surgical intervention	Bypass time	Cross-clamp time	Circulatory arrest time	Weight, kg	Ventilatory support, days	ICU stay, days
1	14	TGA, CoA, VSD; arterial switch procedure; VSD left open	1:17	0:32	0	3.5	9	12
2	29	TOF with pulmonary valve agenesia; ventilator weaning after birth impossible; primary repair	2:46	1:19	0:15	2.6	9	14
3	211	HLHS, MA, VSD, intermittent aortic arch; Fontan completion using a left carotid artery flap	2:45	0	0:16	6.3	19	47
4	7	TGA with patent arterial duct; arterial switch procedure	3:15	1:06	0	3.3	6	25
5	16	HLHS with spongious left ventricular sinusoids, aortic atresia and MA; modified Norwood procedure	2:38	0	0:41	3.1	50	87
6	113	d-TGA with large VSD, pulmonary artery closed after Blalock-Taussig shunt; arterial switch procedure	2:16	1:04	0	4.6	10	23
7	54	Bland-White-Garland-syndrome with LCA from the LPA; Takeuchi operation	3:09	0	0:55	4.8	5	6

TGA, transposition of the great arteries; CoA, coarctation of the aorta; VSD, ventricular septal defect; TOF, tetralogy of Fallot; MA, mitral valve atresia; HLHS, hypoplastic left heart syndrome; LCA, left coronary artery; LPA, left pulmonary artery

Results

The patient characteristics are shown in Table 1; weight was 4.0 ± 1.4 kg, age ranged from 7 to 211 days (median 29) days, ventilator support from 5 to 50 days (median 9) days, and the length of ICU stay from 6 to 87 days (median 23 days). The administration of Levosimendan was not associated with any adverse hemodynamic effect in the study group. The hemodynamic data and inotropic support during Levosimendan infusion are shown in Table 2. The heart rate, mean arterial blood pressure, and central venous pressure were not influenced by Levosimendan (Table 2). The mean lactate levels decreased significantly at 24 and 48 h compared to 1 h after the onset of infusion. The mean $ScvO_2$ increased significantly at 24 and 48 h after the first infusion in comparison to time point 1 h. Epinephrine support was significantly increased at 6, 12, and 24 h. Forty-eight hours after the start of Levosimendan infusion, the difference was no longer statistically significant (Table 2). As usual, after cardiac operations with extracorporeal circulation and hypothermia, the intensive care staff balanced early postoperatively abnormal levels of serum potassium and hemoglobin. No special effect was noted after Levosimendan application, and neither was it possible to differentiate medication-specific electrocardiogram (ECG) changes such as atrioventricular conduction or QT interval changes from alterations induced by surgery and extracorporeal circulation.

None of the seven children died during the first 21 days after surgery. With regard to the pharmacodynamic properties, particularly of the metabolite of Levosimendan with a persistence of approximately one week [8, 9], adverse effects later on are quite unlikely.

Table 2 Hemodynamics and support with inotrope substances during and after Levosimendan infusion

	0 h	1 h	3 h	6 h	12 h	24 h	48 h
$ScvO_2$ [%]	50 (5)	60 (14)	61 (17)	63 (15)	63 (17)	69 (16)*	73 (7)*
Lactate [mmol l^{-1}]	4.5 (2.4)	5.1 (2.9)	6.1 (3.7)	5.8 (2.6)	4.5 (1.9)	2.6 (0.8)*	1.6 (0.5)*
MAP [mmHg]	56 (16)	54 (12)	59 (9)	64 (9)	57 (7)	56 (6)	61 (5)
CVP [mmHg]	9 (2)	12 (3)	13 (3)	14 (3)	11 (3)	10 (4)	10 (3)
HR [bpm]	164 (27)	174 (18)	183 (19)	190 (25)	181 (21)	181 (21)	165 (27)
Ephedrine [µg kg^{-1} min^{-1}]	0.08 (0.07)	0.11 (0.06)	0.16 (0.06)	0.19 (0.07)*	0.20 (0.08)*	0.20 (0.06)*	0.17 (0.10)
Milrinone [µg kg^{-1} min^{-1}]	0.79 (0.27)	0.71 (0.27)	0.70 (0.22)	0.70 (0.22)	0.70 (0.22)	0.70 (0.22)	0.70 (0.22)

The data are displayed as mean values ($\pm$ SD)

*$p < 0.05$ vs. 1 h, after the start of Levosimendan infusion

$ScvO_2$, central venous oxygen saturation; MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate

Fig. 1 Individual central ve-
nous oxygen saturation (ScvO₂)
after the start of Levosimendan
infusion. The correction applied
for cyanotic patients is described
in the Methods section
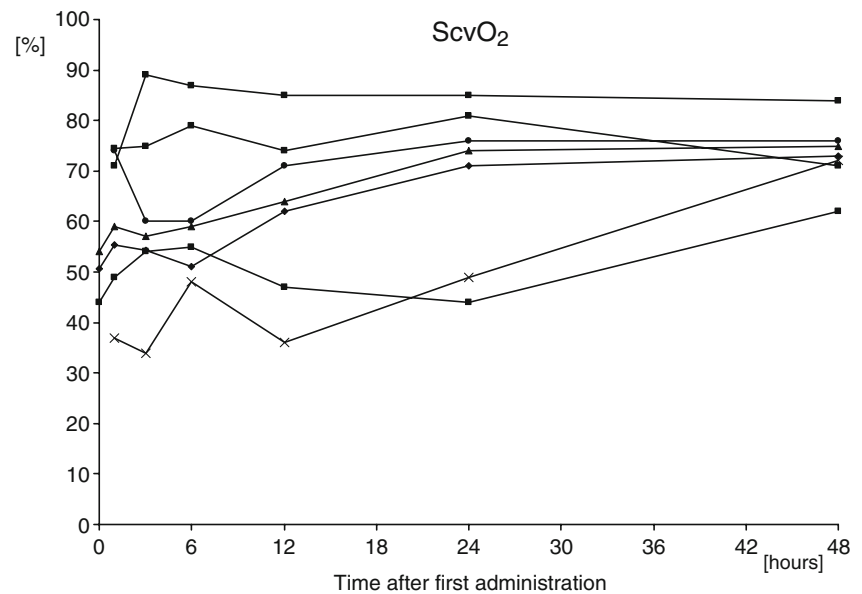
Discussion

The role of Levosimendan as an alternative or supplemental
inotropic agent is still a matter of discussion, especially in
children. So far, randomized prospective clinical studies on
the application of Levosimendan in infants or children are
lacking. The first study investigating Levosimendan in
children was published in 2004 [18]. Thirteen children
between the ages of 3 months and 7 years with congenital
heart disease received a single bolus of 12 μg kg^{-1} during
preoperative cardiac catheterization. The changes of the
hemodynamic variables after this small dose of Levosimen-
dan were not statistically significant. They did not observe
any serious adverse events during the course of the study.

In a retrospective review, Namachivayam et al. proposed
safe use in infants and children with severe myocardial
dysfunction [13]. They reported a substantial reduction of
catecholamines in 15 children with end-stage or acute heart
failure treated in a pediatric ICU.

The time of onset of Levosimendan infusion might be
essential for preventing low cardiac output state after CPB.
In an animal model of infant CPB, Stocker et al. showed
that early treatment with Levosimendan protects from a
reduction in cardiac output (CO), and CO improved above
baseline with Levosimendan [16].

Because of an increasing number of case reports demon-
strating the good safety of Levosimendan even in infants and
children, we started to apply this novel drug in the OR in

Fig. 2 Individual lactate levels
after the start of Levosimendan
infusion
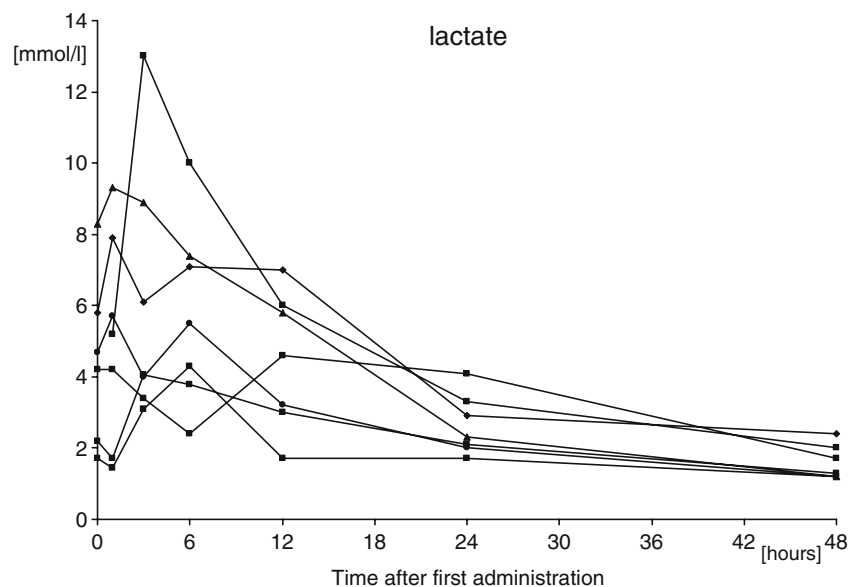
children undergoing complex congenital heart surgery. In our review of seven infants, we found a significant increase of ScvO$_2$ and decrease of lactate levels 24 and 48 h after start of the infusion (Figs. 1 and 2). This indicates an improved cardiac output and oxygen delivery postoperatively. Whether the treated children had a benefit from this drug or not has to be evaluated by further investigations.

Low cardiac output state is a well-recognized phenomenon early after pediatric CPB and is an important risk factor for poor outcome [15]. Only a few investigators have formally measured and evaluated CO during this period because of the known technical problems and adverse effects in small infants. Over a wide hemodynamic range, ScvO$_2$ correlates well to oxygen delivery and cardiac output [14]. The measurement of ScvO$_2$ is simple and does not require additional invasive techniques. In our hospital, ScvO$_2$ is a routinely measured parameter in the OR and in the ICU in order to control the adequacy of oxygen delivery.

We found a significantly increased epinephrine support at 6, 12, and 24 but not at 48 h after the start of Levosimendan infusion. These results are in line with a well known phenomenon in patients with transposition of the great arteries (TGA). In a historic cohort of young infants after arterial switch operation, a decrease in CO has been shown to occur between 3 and 12 h after cross-clamp removal [19]. Three out of our seven patients received an arterial switch operation due to TGA.

In a recent investigation in 45 adults, Tasouli et al. demonstrated the clear superiority of a Levosimendan infusion starting in the OR in comparison with a start in the ICU [17]. Not only did the monitored hemodynamic status of patients improve, in addition, the length of ICU stay and hospitalization was shortened and a trend towards better outcome was found. According to these results and our own experiences, we implemented Levosimendan in our stepwise multimodal protocol for the early treatment and prevention of a low cardiac output state. The steps consist of low-dose catecholamines, vasodilatators, phosphodiesterase inhibitors, and calcium sensitizers. Since Levosimendan is a relatively expensive drug, we consider its use at present as one of the last steps before putting the patients on an ECMO. A proposal aiming at a special cost compensation of Levosimendan use has been submitted to the central German Institute for the Hospital Remuneration System (InEK).

In conclusion, intraoperatively administered Levosimendan was well tolerated in seven infants with severe myocardial dysfunction after complex congenital heart surgery. No adverse effects were observed during and up to 48 h after infusion. Its administration was associated with a significant increase of central venous oxygen saturation and decrease in lactate 24 and 48 h after the start of infusion, indicating an improved cardiac output, thus, improving oxygen delivery. Levosimendan is a new rescue drug for low cardiac output, whose off-label use might also be beneficial in selected cases in pediatric cardiac surgery. The role of intraoperatively and prophylactically administered Levosimendan warrants formal, prospective, and comparative evaluation.

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