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ORIGINAL ARTICLE

# Use of Levosimendan in Postoperative Setting After Surgical Repair of Congenital Heart Disease in Children

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**Abstract** Low cardiac output is one of the most common complications after cardiac surgery. Levosimendan, a new inotrope agent, has been demonstrated in adult patient to be an effective treatment for this purpose when classical therapy is not effective. The aim of this study was to evaluate the effect of Levosimendan on cardiac output parameters in cardiac children with low cardiac output syndrome (LCOS.). We carried out a retrospective analysis on 62 children hospitalized in our pediatric intensive care unit (PICU) after cardiac surgery, which demonstrated LCOS not responding to classical catecholamine therapy and who received levosimendan as rescue therapy. LCOS parameters like diuresis, central venous oxygen saturation ($SvO_2$), venous-to-arterial $CO_2$ difference ($\Delta avCO_2$), and plasmatic lactate were compared before therapy and at 3, 6, 12, and 24 h after the beginning of the levosimendan infusion. We also analyzed the effect on the Vasoactive-inotropic score (VIS), adverse events, and mortality. After the beginning of levosimendan infusion, diuresis (1.1 vs. 3.5 ml/kg/h, $p = 0.001$) and $SvO_2$ (59.5 vs. 63.3%, $p = 0.026$) increased significantly during the 24 h of infusion, and at the same time, plasmatic lactate (2.3 vs. 1.3 mmol/l, $p < 0.001$) decreased. $\Delta avCO_2$ (10.8 vs. 9.4 mmHg, $p = 0.21$) and the VIS (44.5 vs. 22.5, $p = 0.143$) also decreased, but not significantly. No side effects were noted. The mortality in this patient group was 16%. Levosimendan is an effective treatment in children presenting LCOS after congenital heart surgery. Our study confirms the improvement of cardiac output already shown in other pediatric studies, with no undesirable side effects.

**Keywords** Low cardiac output syndrome · Critically ill children · PICU · Levosimendan

## Introduction

Low cardiac output syndrome (LCOS) is a severe complication after cardiac surgery. It occurs in up to 25% of pediatric patients and contributes significantly to patient morbidity and mortality [1, 2]. Cardiopulmonary bypass and cardioplegia induce ventricular dysfunction after heart surgery secondary to myocardial ischemia and the activation of an uncontrolled inflammatory cascade, leading to LCOS. In the context of congenital heart surgery in children, the risk factors increasing the probability of LCOS are well known. Age at surgery, bypass time, aortic cross-clamp time, and the type of surgery are the most frequent cited risks of LCOS in the postoperative period [3, 4]. Contrary to the adult patient, the monitoring of cardiac output after congenital heart surgery in the pediatric population is much more difficult. In the absence of a reliable and safe continuous monitoring device validated in this population, the evaluation of cardiac output relies on clinical evaluation and measurement of surrogate parameters such as urine output, lactate levels, central venous oxygen saturation, and arteriovenous differences in $pCO_2$.

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Currently, the standard treatment of LCOS is based on catecholamine and milrinone administration. Although efficient, these treatments, especially catecholamine, may be deleterious for the myocardium at a cellular (metabolic) level, by increasing its oxygen consumption. Levosimendan is an inotropic agent first described in the early 1990s [5, 6]. It works as a calcium sensitizer, improving the affinity of troponin C for calcium, thus enhancing cardiac contraction and relaxation [6–8]. By its specific cellular effect, levosimendan does not raise cyclic adenosine monophosphate in the myocytes, and by so doing does not increase intracellular calcium. Hence, cardiac function is improved without increasing oxygen consumption by cardiomyocytes and thereby avoiding well-known side effects of phosphodiesterase III inhibitors and catecholamine. This unique pharmacological mechanism of action makes it a fascinating drug to administer in patients with an already failing myocardium. Levosimendan also has vascular effects by opening adenosine triphosphate-dependent potassium channels of systemic, pulmonary, and coronary smooth muscle cells [9–12].

Adult studies have shown that levosimendan enhances systolic and diastolic functions in patients with ventricular dysfunction of all causes when given in addition to a maximal conventional treatment [7, 8]. After cardiopulmonary bypass (CPB), a beneficial effect of levosimendan has also been suggested when given to patients in cardiogenic shock or altered cardiac function in the stunned myocardium [13, 14]. A double-blind study in adult patients after cardiac surgery with bypass has shown hemodynamic improvement and decreased mortality with levosimendan therapy compared with dopamine [15]. Finally, a randomized double-blind trail on 61 patients developing clinical signs of heart failure within 48 h after a primary PCI-treated STEMI showed an improved contractility in postischemic myocardium [16]. However, ambulatory treatment with levosimendan in 120 adults with advance heart failure has shown no significant improvement of functional capacity or quality of life compared with placebo [17].

Levosimendan pharmacokinetics and pharmacodynamics are similar both in children and in adults [18]. Published reports evaluating the beneficial effects of levosimendan in the pediatric population are promising. However, most of these are case reports or retrospective studies with small group samples [19–23].

Since 2005, levosimendan has been used in our pediatric intensive care unit (PICU) as a rescue therapy in patients presenting with LCOS following heart surgery with CPB. The aim of this study is to evaluate the effects of levosimendan on cardiac output parameters when standard treatment failed to stabilize LCOS.

## Methods

This is a retrospective descriptive study on the use of levosimendan in the PICU of Lausanne University Hospital between December 1, 2005 and December 31, 2013. The Lausanne University Hospital is a tertiary care teaching center with approximately 250 congenital open heart surgeries per year.

### Study Design and Patients

Demographic and clinical data were collected from the intensive care database (Metavision®, iMDSoft). Children (0–16 years) were included if they had received levosimendan for LCOS within 48 h after CPB. The senior physician in charge at the PICU defined LCOS based on clinical evaluation of the patient and the dynamic evolution of the surrogate parameters reflecting cardiac output, particularly the following trend in parameters: a decrease in urine output, a decrease in central venous oxygen saturation ($SvO_2$), an increase in the arteriovenous difference in $pCO_2$ ($\Delta avCO_2$), or an increase in lactate levels. The physician also took into account the trend of vasopressor support (norepinephrine and dopamine) necessary to achieve a suitable cardiac output in addition to standard therapy, with milrinone given in all patients. Levosimendan was administered as a rescue therapy, without a bolus, by continuous infusion at 0, 1mcg/kg/min for 48 h. When well tolerated, the dosage was increased to 0, 2 mcg/kg/min, and in that case, for a total of 24 h.

For the purpose of the study, we used the Vasoactive-Inotropic Score (VIS) which is calculated as follows: Dopamine (mcg/kg/min) + Dobutamine (mcg/kg/min) + [100 × Epinephrine (mcg/kg/min)] + [10 × Milrinone (mcg/kg/min)] + [10,000 × Vasopressin (U/kg/min)] + [100 × Norepinephrine (mcg/kg/min)] [24]. From the intensive care database, parameters were collected at time (T) 0, before initiation of levosimendan infusion, and then at 3, 6, 12, and 24 h after the beginning of the infusion.

We used the Pediatric Risk of Mortality Score (PRISM) for pediatric ICU mortality risk assessment and the Risk-Adjusted classification for Congenital Heart Surgery (RACHS) for the classification of surgical mortality risk.

### Statistical Analysis

Data are presented as median with interquartile range for continuous variables and *N* (%) for categorical variables. LCOS parameters were compared using an ANOVA for multiple-paired values. For statistical analysis, we used

Stata 13.1 version. A $p$ value of $<0.05$ was considered significant.

## Results

Demographic data (Table 1): 62 patients were included in the study, 25 girls (40%) and 37 boys (60%). Due to their hemodynamic instability, all patients were mechanically ventilated, received appropriate sedation and analgesia, and were paralyzed in order to be kept on a refrigerated mattress. Our studied population was quite young: ages ranged from a few hours to 14 years old [median 0.5 years old (0.03–2.8)]. Median pediatric intensive care unit (PICU) length of stay was 13.0 days [7.0–22.0], and the median mechanical ventilation days were 7.0 days [4.0–10.0]. Median PRISM was 8.0 [5.0–12.0]. Median bypass time was 176 min [146–229], and median aortic cross-clamp was 92 min [66–113]. Two children had no aortic cross-clamp. Major diagnostic groups included univentricular hearts (32.3%), transposition of great arteries (21%), Tetralogy of Fallot (11.3%), and double outlet right ventricle (11.3%). Two patients received levosimendan after a heart transplant. RACHS score was 3 in 43.3% of the patients, the remainder of the patients had RACHS scores of 2 and 4 (respectively, 28.4 and 23.3%) (Table 1). Forty patients (65%) were less than one year old, with a prolonged CPB [median 175 min (147–217)] and aortic cross-clamp time [median 75 min (56–112)]. Levosimendan was started between 1.3 and 47.4 h after the end of the CPB [median 14.4 h (5.6–25.2)].

**Table 1** Demographic data

| | $N = 62$ |
|---|---|
| Age (years) | 0.5 [0.03–2.8] |
| Weight (kg) | 5.7 [3.5–11.4] |
| Sex ♀/♂, (%) | 25/37 (40/60%) |
| Bypass time (min) | 176 [146–229] |
| Aortic clamping time (min) ($N = 60$) | 92 [66–113] |
| RACHS 1 (%) | 1 (1, 6%) |
| RACHS 2 (%) | 17 (28.4%) |
| RACHS 3 (%) | 26 (43.3%) |
| RACHS 4 (%) | 14 (23, 3%) |
| RACHS 6 (%) | 2 (3, 4%) |
| PRISM score | 8 [5–12] |
| LOS (days) | 13 [7–22] |
| MVD (days) | 7 [4–10] |
| Mortality (%) | 10 (16%) |

Data are expressed as *N* and percent or median and IQR. Two patients with heart transplant and no RACHS score

*RACHS* risk-adjusted classification for congenital heart surgery, *PRISM* pediatric risk of mortality score, *LOS* length of stay, *MVD* mechanical ventilation days

Outcome analysis: the ANOVA demonstrated that cardiac output parameters improved during levosimendan infusion: diuresis increased significantly from 1.1 ml/kg/h [0.6–2.3] to 3.5 ml/kg/h [2.1–5.6] ($p = 0.001$). $SvO_2$ increased significantly from 59.5% [47.3–66.4] to 63.3% [55.8–71.5] ($p = 0.026$). Lactate decreased significantly from 2.3 mmol/l [1.3–4.5] to 1.3 mmol/l [1.1–1.9] ($p < 0.001$). The $\Delta avCO_2$ decreased from 10.8 mmHg [8.4–13.3] to 9.4 mmHg [7.6–12.1] ($p = 0.21$). The VIS decreased from 44.5 [23.8–99.7] to 22.5 [9–45] at 24 h ($p = 0.143$). The decreases in both latter parameters were nonsignificant. Figure 1 summarizes these results.

Levosimendan infusion was extremely well tolerated, with no significant side effects, and particularly no arrhythmia or hypotension. Interestingly, levosimendan prescription has increased over the years, whereas mortality in this group of patient decreased over the same time period (Fig. 2).

Four children needed extracorporeal membrane oxygenation. Of these, three children (4.8%) were admitted to the PICU on ECMO due to severe myocardial dysfunction and failure of weaning off cardiopulmonary bypass, whereas one child (1.6%) was put on ECMO in the PICU because of intractable LCOS despite the introduction of levosimendan. Two (50%) of the children on ECMO died because of ischemic or thromboembolic complications.

Mortality was 16%, ten of the 62 patients included in this study, whereas overall mortality of pediatric cardiac surgery patients in our institution during that same period was 3.1%. Nine of these 10 patients (90%) were under 1 year old. Seven patients (7/10) died in the immediate postoperative period (30 days mortality 11.3%). Causes of death, in the latter group, were multiple organ failure (1/7), cerebral hemorrhage (2/7), ischemic brain death (1/7), severe thromboembolic events under ECMO (1/7,) hemorrhagic shock (1/7), and refractory ventricular dysfunction (1/7). The other three patients (3/10) died after 30 days of PICU due to cardiac and noncardiac complications.

## Discussion

The purpose of this study was to evaluate the effects of levosimendan as a rescue therapy on cardiac output parameters in children following cardiac bypass. Based on our results, levosimendan stabilizes and even improves most cardiac output parameters in patients when the usual inotropic treatments failed.

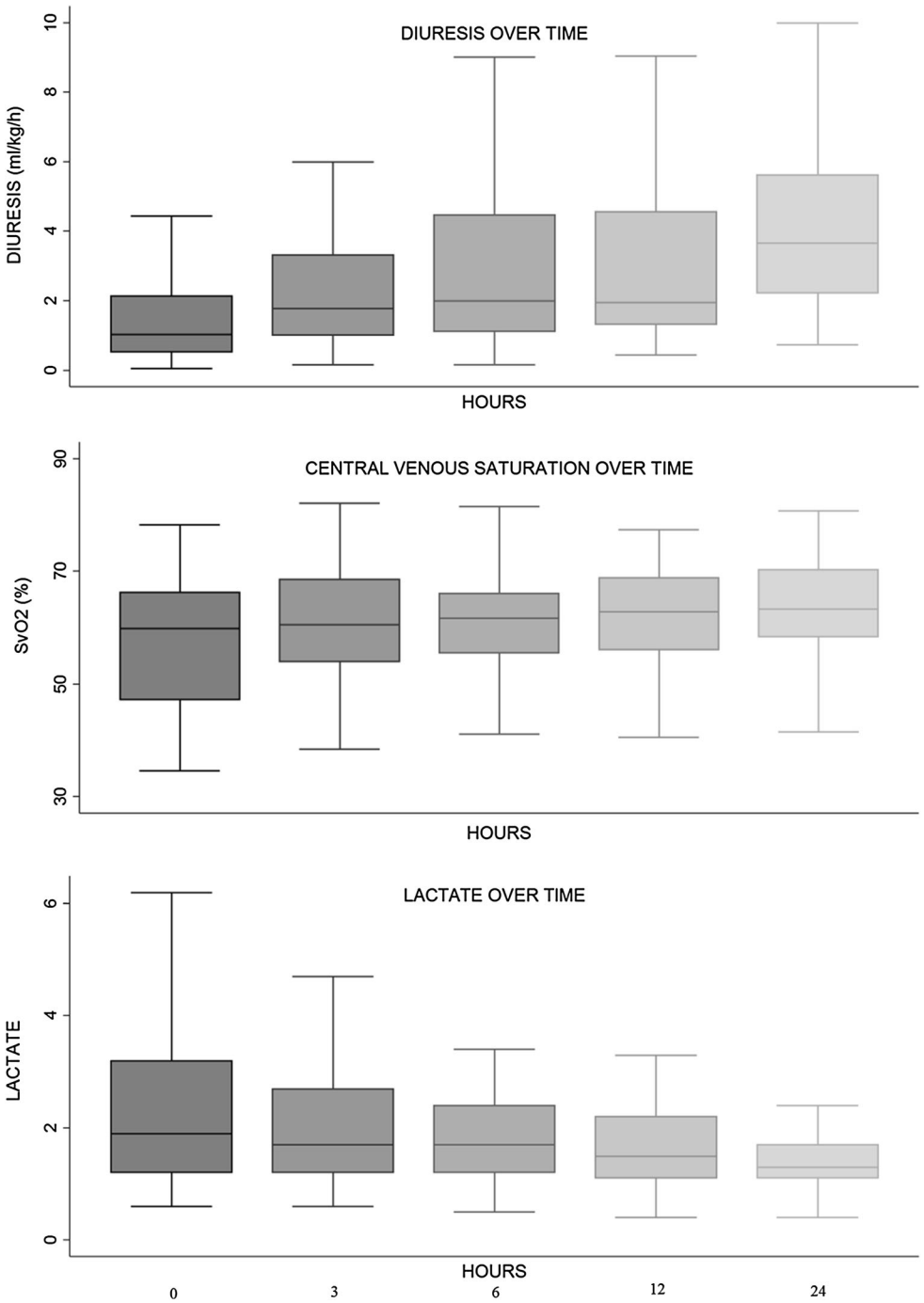


**Fig. 1** Median with interquartile range (*box plot*) and minimum and maximum values (*lines*) of diuresis, central venous oxygen saturation, and lactate at time 0, before initiation of levosimendan infusion, and then at 3, 6, 12, and 24 h after the beginning of the infusion

As frequently encountered in studies concerning children with congenital heart disease, our studied population is heterogeneous regarding ages and regarding congenital heart defect diagnosis. As would be expected, most of the patients included in the study and receiving levosimendan were newborns or infants with prolonged bypass and aortic cross-clamp times and high RACHS scores, a high-risk group for developing LCOS [3, 4]. Overall mortality in this patient group was therefore higher compared to the overall mortality rate of pediatric cardiac surgery patients in our institution. Interestingly, we have observed that the mortality rate, in our patients treated with levosimendan, has decreased over the years. This may be explained by the increasing PICU physician's familiarity with levosimendan and consequently, a progressively earlier initiation of the levosimendan in the postoperative period. In our experience, levosimendan is extremely well tolerated. We did not

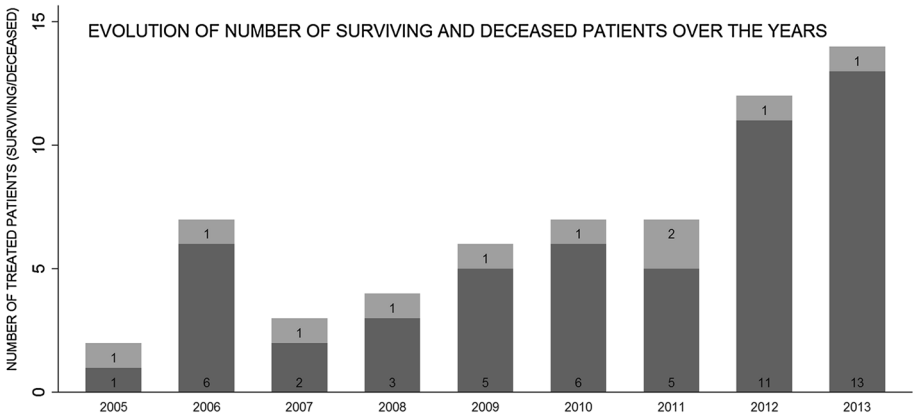


**Fig. 2** Evolution of the number of patients treated over time. The *dark gray block* represents the surviving patients, the *light gray blocks*, the deceased patients

observe any adverse events that could be attributable to levosimendan in our patients.

Our study is one of the largest studies relating the efficacy of levosimendan in children with LCOS after cardiac bypass. LCOS remains a major complication after congenital heart surgery. Our results confirm those of other pediatric studies. Eggan et al. examined the effects of levosimendan administered in 19 children, either before the end of the cardiopulmonary bypass, if low cardiac output was expected, or when cardiac dysfunction refractory to conventional inotropic therapy appeared [21]. Their results showed a significant decrease in lactate levels during and after levosimendan infusion, as in our group of patients. Contrary to our findings and probably due to the small number of patients in their study, the other surrogate parameters of cardiac output did not differ significantly. However, they observed a significant reduction in inotropic support following levosimendan infusion, which we could not demonstrate. It is worthy to note that the mortality rate was really high (27%) in their studied group of patient compared with their usual mortality rate (1.8%). In a retrospective review of 15 children, Namachivayam et al. also observed a significant decrease in inotropic support after levosimendan administration in patients presenting with severe cardiac dysfunction refractory to maximal catecholamine treatment. Although without statistical significance in their study, levosimendan improved ejection fraction and led to a reduction or withdrawal of catecholamine and reduced lactate levels [22]. In 2012, Ricci et al. compared the outcomes of two groups of newborns after congenital heart surgery, one group receiving 72 h of continuous levosimendan infusion, given at 0, 1 mcg/kg/min, while the other group received a standard inotropic regimen (dopamine, milrinone) after CPB [25]. Their results demonstrated a more rapid decrease in lactate levels in the levosimendan-treated group, with a statistically significant decrease at admission and 6 h after admission in the PICU.

Levosimendan infusion was, in our study, most frequently started within the first 24 h after bypass at a time when LCOS is known to appear or worsen. The benefits of levosimendan were clinically apparent 6–12 h after the initiation of therapy as observed by other authors [19, 20, 25]. In our experience, in selected high-risk patients for postoperative LCOS, administration of levosimendan, either after cardiopulmonary bypass weaning or as early as 24 h preoperatively may prevent or drastically reduce the severity of LCOS. Hence, for a few years, it has been our practice to initiate levosimendan infusion 24 h before heart surgery in selected cases, particularly in newborns or before an elective complex heart surgery. In the early postoperative period, we consider levosimendan therapy when faced with failure of CPB weaning or when inotropic, and catecholamine support during CPB weaning is already substantial. We have observed that the efficacy and benefits of levosimendan, administered in a "preventive" manner, appear to be superior compared to those when it is initiated once LCOS is clinically manifest. These impressions need, however, to be confirmed in randomized controlled studies. Some studies in adults indeed have confirmed the superior efficacy of levosimendan when given in the preoperative setting, prior to the onset of the myocardial insult induced by CPB [26–28].

The pharmacological effects of levosimendan are prolonged, and may last several days after infusion. Enhancements in both systolic and diastolic functions without increasing the heart's oxygen consumption make levosimendan an attractive therapy for heart failure regardless of its origin [29, 30].We have been using levosimendan since many years to treat children with uncompensated heart failure of various etiologies. It helps stabilize the patients condition and, in some cases, contributes to the patient's recovery. Thereby, the need for mechanical cardiac support is at times avoided. When mechanical cardiac support is, despite everything, necessary, levosimendan therapy allows for a faster withdrawal

of the mechanical support, as also described by Suominen et al. [23]. In our opinion, levosimendan will undoubtedly be admitted as a standard therapy in the management of pediatric heart failure, particularly in the cardiac surgery setting, where cardiac ischemic and inflammatory injuries are induced.

The use of levosimendan is safe in the pediatric population, particularly in infants, newborns, and even premature babies. We did not come across any side effects that could be attributed to its use—findings that are consistent with many reports in the literature [18, 22, 25]. A case report, published by Lechner et al., describes levosimendan administration in a premature neonate (32 weeks gestational age) presenting severe left ventricular dysfunction after cardiac surgery, despite high-dose catecholamine administration and in whom extracorporeal membrane oxygenation was not an option due to low birth weight (1525 gr). After initiation of levosimendan infusion, a gradual recovery of left ventricular function was observed, with no side effects [19].

Our study has some methodological limitations. First of all, the retrospective and uncontrolled nature of the study makes it less statistically powerful than a randomized controlled one, and our results can be criticized in this respect. The heterogeneity of the population studied, regarding ages, diagnosis, and type of surgery, makes it difficult to make generalization of our conclusions to every patient in the postoperative period. Despite the fact that our study is among the largest pediatric studies, the number of patients remains weak compared with similar adult studies. In our study, levosimendan treatment was used as a rescue therapy when faced with a patient with LCOS in the postoperative setting. The decisions on when to initiate treatment, the infusion rate, and the duration of treatment were taken by the physician in charge of the patient and were therefore a matter of a clinical decision. There were no specific criteria or treatment protocols followed for defining LCOS and regarding when levosimendan infusion should be started, making the validity of our results difficult to be generalized in another set-up. Our study demonstrates that the use of levosimendan in children after CPB is effective and harmless. Nevertheless, further evidence validating the safety, the use, and the benefits of levosimendan in children must still be brought forth, ideally through more prospectively controlled studies.

In conclusion, levosimendan, when used as a rescue therapy, improves cardiac output parameters in children presenting with LCOS after cardiac surgery for congenital heart disease. In accordance with other pediatric studies done in similar settings, Levosimendan is demonstrated to stabilize the hemodynamic condition of the patient and may avoid the need for mechanical cardiac support, although this has to be confirmed by further studies. This treatment is well tolerated, even in very young children, with no undesirable side effects. Early levosimendan initiation in the postoperative period appears to impact positively on patients' outcomes. In certain high-risk patients, preoperative treatment should be considered. Levosimendan is a cardioprotective drug that will undoubtedly become part of the standard of care of the prevention and management of LCOS.

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**Compliance with Ethical Standards**

**Conflict of interest** The authors declares that there is no conflict of interest.

**Ethical Approval** All procedure performed in this study involving human participants were in accordance with the ethical standards of the institutional research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Informed Consent** For this type of study formal consent is not required.

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