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Original Article

Role of Levosimendan in Post-operative Low Cardiac Output Management in Children

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Abstract

Objectives: Low cardiac output syndrome (LCOS) is a critical complication following pediatric cardiac surgery that is characterized by myocardial dysfunction, hemodynamic instability, and insufficient organ perfusion. Levosimendan, an inotropic agent that enhances calcium sensitivity in cardiac muscle and causes vasodilation, has been proposed as a therapeutic option for managing LCOS in children. This study aimed to evaluate the efficacy and safety of levosimendan in the 23 management of LCOS in pediatric patients following cardiac surgery.

Methods: This study retrospectively included patients who underwent surgery in our clinic between 2020 and 2023 and received levosimendan due to post-operative LCOS. The patients' medical records were accessed through the hospital information system and archival review.

Results: The median age of the patients was 8 months (interquartile range: 5.0–16.0 months). Post-operative echocardiographic assessments revealed a significant improvement in ejection fraction, with a median increase from 40.0% to 57.5% in survivors ($p<0.001$). No significant difference in mortality, intensive care unit stay, or hospital stay was observed between survivors and non-survivors, although non-survivors had a higher post-operative heart rate ($p=0.025$). Levosimendan was well tolerated, with minimal adverse effects, and no arrhythmias were recorded. Hypotension was effectively managed with norepinephrine.

Conclusion: Levosimendan appears to be an effective and safe treatment option for managing LCOS in pediatric patients after cardiac surgery. While the drug significantly improved cardiac function, further large-scale studies are necessary to evaluate its long-term efficacy and safety. Individualized dosing and careful monitoring are essential to optimize patient outcomes.

Keywords: Ejection fraction; inotropic agents; levosimendan; low cardiac output syndrome; pediatric cardiac surgery.

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Çocuklarda Ameliyat Sonrası Düşük Kardiyak Debi Yönetiminde Levosimendan'ın Rolü

Özet

Amaç: Düşük kardiyak debi sendromu (LCOS), pediatrik kalp cerrahisi sonrası gelişebilen, miyokardiyal disfonksiyon, hemodinamik instabilite ve yetersiz organ perfüzyonu ile karakterize kritik bir komplikasyondur. Kardiyak kaslarda kalsiyum duyarlılığını artıran ve vazodilatasyona yol açan bir inotropik ajan olan levosimendan, çocuklarda LCOS yönetiminde terapötik bir seçenek olarak önerilmektedir. Bu çalışmanın amacı, pediatrik hastalarda kalp cerrahisi sonrası gelişen LCOS yönetiminde levosimendanın etkinliğini ve güvenliğini değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya, 2020–2023 yılları arasında kliniğimizde ameliyat edilen ve postoperatif düşük kardiyak debi sendromu (LCOS) nedeniyle levosimendan tedavisi alan hastalar dâhil edildi. Hastaların tıbbi kayıtlarına, hastane bilgi sistemi ve arşiv taraması ile ulaşıldı.

Bulgular: Hastaların medyan yaşı 8 aydı (IQR: 5,0–16,0 ay). Postoperatif ekokardiyografik değerlendirmelerde, sağ kalan hastalarda ejeksiyon fraksiyonunda (EF) anlamlı bir iyileşme görüldü; medyan EF %40,0'dan %57,5'e yükseldi (p<0,001). Sağ kalanlar ile sağ kalamayanlar arasında mortalite, yoğun bakımda kalış süresi veya hastanede kalış süresi açısından anlamlı fark bulunmazken, sağ kalamayanlarda postoperatif kalp hızı daha yüksek saptandı (p=0,025). Levosimendan iyi tolere edildi, minimal yan etki gözlendi ve aritmi kaydedilmedi. Hipotansiyon, norepinefrin ile etkin şekilde yönetildi.

Sonuç: Levosimendan, pediatrik hastalarda kalp cerrahisi sonrası LCOS yönetiminde etkili ve güvenli bir tedavi seçeneği olarak görünmektedir. İlaç, kardiyak fonksiyonlarda anlamlı iyileşme sağlasa da, uzun dönem etkinlik ve güvenliğini değerlendirmek için daha geniş ölçekli çalışmalara ihtiyaç vardır. Hastaya özel dozlama ve dikkatli izlem, hasta sonuçlarını optimize etmek için kritik öneme sahiptir.

Anahtar sözcükler: Ejeksiyon fraksiyonu; inotropik ajanlar; levosimendan; düşük kardiyak debi sendromu; pediatrik kalp cerrahisi.

Introduction

Low cardiac output syndrome (LCOS) can lead to severe clinical conditions, especially when it occurs after pediatric cardiac surgery. Post-operative LCOS is a result of myocardial dysfunction, hemodynamic instability, and inadequate organ perfusion. This condition can cause organ damage and potentially lead to multiple organ failure due to insufficient oxygenation and an inability to meet metabolic demands. The consequences of LCOS include renal failure, neurological damage, gastrointestinal ischemia, and the need for prolonged intensive care. In addition, if LCOS is not treated promptly and effectively, it significantly increases mortality rates.[1,2]

Levosimendan is a drug that increases myocardial contractility by increasing calcium sensitivity through binding to troponin C in cardiac muscle cells. It also opens ATP-sensitive potassium channels, leading to vasodilation in both coronary arteries and the peripheral vascular system. Owing to this dual-action mechanism, levosimendan increases cardiac output while reducing systemic vascular resistance and minimally increasing myocardial oxygen consumption. This makes it an ideal option for managing the LCOS, as its inotropic and vasodilatory effects help maintain hemodynamic stability.[3,4]

While levosimendan presents a significant treatment option, particularly in cases of refractory low cardiac output, careful patient monitoring and management of side effects are crucial during its use. The literature on the use of levosimendan in the treatment of LCOS in pediatric patients reports both positive outcomes and concerns regarding various side effects.[5,6] Therefore, this article aims to review the effects and clinical use of levosimendan in pediatric patients with LCOS, present our own experience and provide a foundation for future research.

Materials and Methods

This study retrospectively included 21 patients who underwent surgery in our clinic between 2020 and 2023 and received levosimendan (Simdax, Orion Corporation, Finland) due to post-operative LCOS. The patients' medical records were accessed through the hospital information system and archival review.

This study was approved by the Ethics Committee of Liv Bona Dea Hospital (Date: 07/2025; Protocol No: 183). All procedures were carried out in accordance with ethical standards.

Echocardiography (Epiq 7; Philips, Amsterdam, The Netherlands, and Vivid E95; GE Healthcare, Chicago, IL) was performed regularly in the pre-operative, post-operative, and post-medical treatment phases. Ejection fraction (EF) values were calculated via EPSS (E-Point Septal Separation), a method for measuring the distance between the anterior mitral valve leaflet and the interventricular septum in early diastole. The EF was measured through Simpson's single-plane method, and cardiac output was obtained through the Doppler-VTI method.

LCOS was defined as meeting at least two of the following criteria, along with a mean invasive arterial blood pressure below the 5th percentile (based on a nomogram adjusted for height and age), after achieving adequate preload:[7]

- Arterial lactate levels >3 mmol/L in two consecutive measurements,
- A mixed venous oxygen saturation ($ScvO_2$) <50% or a decreasing trend was detected,
- The urine output was <1 mL/kg/h for 2 consecutive h,
- Heart rate >90th percentile according to an age-based nomogram.

In the early post-operative period, balanced general anesthesia was provided via fentanyl and midazolam infusions.

Surgical Procedure

All patients were started on milrinone at a dose of 0.5 mcg/kg/min after standard induction, intubation, and catheterization. Following surgical exposure, cardiopulmonary bypass (CPB) was initiated. Del Nido or cold blood cardioplegia was used to achieve cardiac arrest in all patients. The target mean arterial pressures during and after CPB were 30 mmHg and 45 mmHg, respectively. In addition, the target serum hemoglobin level was maintained above 100 g/L, the serum lactate level was <2 mmol/L, and the ionized calcium level was >1.2 mmol/L. A hypothermia of 32°C was used. Upon weaning from CPB, adrenaline infusion was added to milrinone if necessary.

Low Cardiac Output Monitoring

All patients were followed with invasive arterial monitoring, and continuous CVP values were monitored via a central venous catheter. Pulse oximetry and electrocardiography were continuously monitored. Arterial blood gas analysis was performed at regular intervals to evaluate metabolic and respiratory parameters. Hourly urine output was monitored via urinary catheters in all patients.

Levosimendan was initiated in patients with reduced left ventricular (LV) contraction and decreased EF/LV function on early post-operative echocardiography, in addition to other LCOS parameters. After starting levosimendan, the milrinone dose was reduced to a minimum. If hypotension occurred, milrinone was discontinued, and a norepinephrine infusion was added to the treatment.

For levosimendan preparation, 12.5 mg (5 mL) of the drug was dissolved in 45 mL of 5% glucose. An initial dose of 0.1 µg/kg/min was started, which was increased to 0.2 µg/kg/min depending on the patient's blood pressure. The infusions were continued for 48 h. Attending physicians were given full discretion to administer additional medications, including other inotropes and vasopressors, as appropriate. The simultaneous use of nesiritide was not allowed. Calcium levels were closely monitored and maintained within the ideal range through frequent blood gas checks.

Morbidities, ventilation duration, intensive care unit (ICU) stay, and total hospital stay were also recorded.

The study was conducted retrospectively with approval from hospital management and in accordance with ethical guidelines, following the principles of the Helsinki Declaration.

Statistical Analysis

Statistical analysis was performed through SPSS version 27 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as frequencies and percentages, whereas numeric variables are presented as the means, standard deviations, medians, 25th percentiles, and 75th percentiles. Normality will be assessed through skewness and Shapiro–Wilk tests. Student's t-test will be used to compare means between two independent groups for normally distributed data. For nonnormally distributed data, the Mann–Whitney U test will be used to compare medians between two independent groups, and the Wilcoxon test will be used to compare medians between two dependent groups. The Chi-square test or Fisher's exact test will be used to compare categorical variables between independent groups. A $p<0.05$ was considered to indicate statistical significance.

Results

This study included 21 pediatric patients who underwent cardiac surgery and received levosimendan. The median age of the patients was 8.0 months (interquartile range [IQR]: 5.0–16.0 months), with 7 patients (33.3%) being female. The surgical procedures performed on these patients were as follows: 6 patients (28%) underwent the arterial switch procedure, 5 patients (24%) underwent VSD closure, 3 patients (14%) underwent AVSD repair, 2 patients (9%) underwent pulmonary valvotomy, 1 patient (5%) underwent dual-chamber pacemaker implantation, 1 patient (5%) underwent truncus repair, 1 patient (5%) underwent complete TOF repair, 1 patient (5%) underwent ALCAPA repair, and 1 patient (5%) underwent Glenn + pulmonary banding surgery.

Among the patients, 14 (66.7%) received Del-Nido cardioplegia, while 7 (33.3%) were given cold blood cardioplegia. The median weight of the cohort was 4.6 kg (IQR: 3.75–7.0 kg). The detailed baseline characteristics, including mechanical ventilation time, ICU stay, and hospital stay, are presented in Table 1. The median duration of mechanical ventilation was 49.0 h (IQR: 24.0–74.0 hours), the median ICU stay was 7.0 days (IQR: 5.0–10.0 days), and the median hospital stay was 15.0 days (IQR: 12.0–18.0 days).

Table 1. Baseline characteristics

Variable	Category	n (%)/Median (IQR)
Gender	Female	7 (33.3)
	Male	14 (66.7)
Age (months)		8.0 (5.0–16.0)
Weight (kg)		4.6 (3.75–7.0)
Cardioplegia solution	Del Nido	14 (66.7)
	Blood	7 (33.3)
Mechanical ventilation time (hours)		49.0 (24.0–74.0)
ICU stay (days)		7.0 (5.0–10.0)
Hospital stay (days)		15.0 (12.0–18.0)

IQR: Interquartile range; ICU: Intensive care unit.

Table 2. Post-operative variables

Variable	Category	n (%)/Median (IQR)
CPB time (minutes)		98 (79–135)
Cross clamp time (minutes)		76 (51–103)
Mechanical ventilation time (hours)		49.0 (24.0–74.0)
Mortality	Alive	18 (85.7)
	Exitus	3 (14.3)
Levosimendan dosage	Low dosage	6 (28.6)
	Moderate or high dosage	15 (71.4)
Pre-treatment ejection fraction (%)		40.0 (35.0–40.0)
Post-treatment ejection fraction (%)		55.0 (50.0–62.0)
Post-operative troponin (ng/mL)		5.327 (1.410–23.200)
Pre-operative heart rate (bpm)		126 (118–140)
Post-operative heart rate (bpm)		142.0 (134.0–147.0)

IQR: Interquartile range; CPB: Cardiopulmonary bypass.

Intraoperative details, including CPB and cross-clamp times, are summarized in Table 2. The median CPB time was 98 minutes (IQR: 79–135 min), and the median cross-clamp time was 76 min (IQR: 51–103 min). Postoperatively, 18 (85.7%) of the patients survived, whereas 3 (14.3%) died. The majority of the patients (71.4%) received moderate or high doses of levosimendan, whereas 28.6% received low doses.

A comparison of parameters between survivors and nonsurvivors is shown in Table 3. The pre-operative EF was similar between the two groups, with a median EF of 40.0% (IQR: 35.0–40.0%) in survivors and 37.5% (IQR: 35.0–40.0%) in nonsurvivors. Postoperatively, the median EF improved to 57.5% (IQR: 50.0–62.0%) in survivors and 50.0% (IQR: 50.0–64.0%) in nonsurvivors. The difference in EF between the two groups was not statistically significant ($p = 0.720$). However, the post-operative heart rate was significantly greater in nonsurvivors, with a median of 169.5 bpm (IQR: 159.0–180.0 bpm), than in survivors, with a median of 138.0 bpm (IQR: 125.0–145.0 bpm) ($p=0.025$). Other parameters, such as post-operative troponin and creatinine levels, did not differ significantly between the groups.

Table 3. Comparison of parameters between the survivor and nonsurvivor groups

Variable	Category	Alive	Exitus	p
Age (months)		8.00 (4.00–30.00)	6.00 (5.00–9.00)	0.724
Gender (%)	Female	5 (27.8)	2 (66.7)	0.247
	Male	13 (72.2)	1 (33.3)	
Cardioplegia solution (%)	Del Nido	12 (66.7)	2 (66.7)	1.000
	Blood	6 (33.3)	1 (33.3)	
Weight (kg)		4.80 (3.75–7.00)	4.20 (3.00–8.00)	0.615
CPB time (minutes)		98 (82–130)	85 (67–180)	0.832
Cross clamp time (minutes)		80 (50–99)	59 (51–125)	0.958
Mechanical ventilation time (hours)		48.5 (24.0–74.0)	72.0 (20.0–215.0)	0.546
ICU stay (days)		7.0 (5.0–10.0)	8.0 (3.0–10.0)	0.880
Hospital stay (days)		15 (13–18)	8 (7–19)	0.288
Levosimendan dosage (%)	Low Dosage	5 (27.8)	1 (33.3)	1.000
	Moderate or high dosage	13 (72.2)	2 (66.7)	
Pre-treatment ejection fraction (%)		40.0 (35.0–40.0)	37.5 (35.0–40.0)	1.000
Post-treatment ejection fraction (%)		57.5 (50.0–62.0)	50.0 (50.0–64.0)	0.720
Post-operative troponin (ng/mL)		7.385 (1.410–23.200)	5.327 (5.327–5.327)	1.000
Pre-operative heart rate (bpm)		124 (113–134)	145 (140–150)	0.055
Post-operative heart rate (bpm)		138.0 (125.0–145.0)	169.5 (159.0–180.0)	0.025

CPB: Cardiopulmonary bypass, ICU: Intensive care unit.

The effects of levosimendan on pre-treatment and post-treatment EF values are illustrated in the accompanying bar graph. A Wilcoxon signed-rank test was performed to assess the change in EF before and after treatment within the entire cohort. The test statistic indicated a significant improvement in EF postoperatively ($Z=-3.432$, $p<0.001$).

Discussion

Studies evaluating the effectiveness of levosimendan in treating LCOS after pediatric cardiac surgery are crucial for understanding the potential benefits and limitations of this agent. Various clinical trials have demonstrated that levosimendan is effective in reducing the incidence of LCOS. For example, a meta-analysis revealed that the prophylactic use of levosimendan reduced the incidence of LCOS by 20%.[8] In this study, we assessed the potential effects of levosimendan on ventricular systolic function after pediatric cardiac surgery through echocardiography. A statistically significant increase in the LVEF was observed after levosimendan administration. This finding suggests that levosimendan may be more effective in increasing cardiac output than other inotropic agents.

Levosimendan increases myocardial contractility by increasing calcium sensitivity and acts as a phosphodiesterase III inhibitor, leading to vasodilation. These dual mechanisms form the unique pharmacological profile of levosimendan in the treatment of LCOS. The hemodynamic benefits of levosimendan, such as reducing systemic vascular resistance and improving cardiac output in children with LCOS after cardiac surgery, have been supported by studies.[9,10] Hypocalcemia is a common occurrence in patients treated with levosimendan. We aimed to increase the effectiveness of the drug by keeping calcium levels within the optimal range through frequent blood gas checks in patients who received levosimendan.

The positive effects of levosimendan on myocardial function could provide a significant advantage in treating LCOS. By increasing myocardial calcium sensitivity and opening ATP-sensitive potassium channels, it optimizes contractility and causes vasodilation in coronary arteries. This dual action may help achieve hemodynamic stability in pediatric patients after cardiac surgery.[11] While the anti-inflammatory and antiapoptotic effects of levosimendan have been demonstrated in the literature,[12] we did not obtain inflammatory data in this study. However, we believe that the anti-inflammatory effects of levosimendan described in the literature could have positive impacts on post-operative LCOS management.

Levosimendan is contraindicated in patients with severe renal failure. However, studies have shown that the estimated glomerular filtration rate (GFR) is greater in patients treated with levosimendan than in those treated with dobutamine or placebo. In addition to its hemodynamic benefits, levosimendan has direct effects on renal circulation, leading to renal artery vasodilation, thus improving renal blood flow without compromising the oxygen demand/supply relationship.[13] In our series, the GFR and creatinine values remained within normal ranges, and no cases of renal failure were observed.

However, some limitations of levosimendan use should not be overlooked. Clinical studies with this agent show significant variations in dosage, administration methods, and duration, complicating the general interpretation of the results. Higher doses of levosimendan have been associated with potential side effects such as hypotension and arrhythmias, indicating the need for caution when this agent is used. Furthermore, long-term effects and safety profiles require more comprehensive evaluation.[14] In our series, no arrhythmias were observed, but for patients who developed hypotension after starting levosimendan, we administered a norepinephrine infusion to manage it.

Looking at larger studies in the literature, a 2017 international consensus concluded that levosimendan cannot be routinely recommended for cardiac surgery.[15] On the other hand, the 2018 German guidelines on ICU management following cardiac

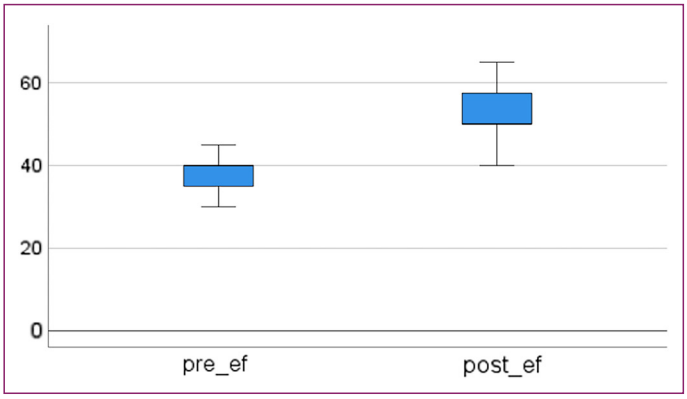

Figure 1. Effects of levosimendan on pre-treatment and post-treatment EF values.

surgery recommended levosimendan for patients with severely impaired LVEF and as the only inotropic agent with proven mortality benefits in LCOS patients.[16] In our clinic, owing to its high cost, levosimendan is not used as a routine inotropic agent but rather for post-operative LCOS treatment.

To avoid potential systemic hypotension, some studies suggest starting levosimendan without a loading dose. The drug can be initiated at the lowest dose (0.05 mcg/kg/min) and increased to doses up to 0.6 mcg/kg/min if needed. The beneficial effects of levosimendan are evident within 24 and 48 h after administration, which is consistent with existing pharmacokinetic data. Its active metabolite, OR-1896, which has similar positive inotropic effects, has an elimination half-life of 80–96 h, which is much longer than that of the parent drug.[17] In our clinical practice, we start levosimendan at a dose of 0.1 mcg/kg/min in LCOS patients and increase the dose to 0.2 mcg/kg/min in the absence of hypotension or side effects. We administer the infusion over 48 h as recommended in the literature.

Lapere et al.[18] reported that, compared with other inotropes or a placebo, the prophylactic use of levosimendan in pediatric cardiac surgery reduced the incidence of LCOS and increased the cardiac index. However, they reported no improvement in mortality, ICU stay, hospital stay, or mechanical ventilation duration. In our study, despite no significant differences in mortality, ICU stay, hospital stay, or mechanical ventilation duration between the patients who survived and those who did not, both groups showed significant improvements in LVEF (Fig. 1). We believe that this may be due to the multifactorial nature of mortality and morbidity in post-operative pediatric cardiac patients.

LCOS is a multifaceted process that often complicates post-operative care following complex cardiac surgeries involving CPB. Pre-operative conditions, intraoperative management, residual lesions, arrhythmias, and factors such as preload, pulmonary and systemic afterload, the neurohormonal axis, systemic inflammation, and increased metabolic disturbances significantly contribute to the development of LCOS. Rapid recognition and correction of low cardiac output, as well as identification of the underlying cause, are critical to reversing the syndrome before cardiovascular collapse. This requires meticulous teamwork among surgeons, pediatric cardiologists, anesthesiologists, and ICU specialists.[19]

Owing to its peripheral vasodilatory effects, Abdelbaser et al.[20] investigated the effectiveness of inhaled versus intravenous levosimendan in reducing high pulmonary artery pressure (PAP) in children undergoing cardiac surgery. They reported that inhaled levosimendan was as effective as intravenous administration in reducing PAP, with fewer side effects, such as tachycardia and hypotension, and reduced vasopressor requirements. Compared with dobutamine infusion in patients with severe decompensated heart failure, levosimendan was found to be superior in reducing pulmonary capillary wedge pressure and mortality at 6 months, although the SURVIVE trial did not show any primary or treatment benefits in severe decompensated heart failure patients.[21,22] Pulmonary hypertension is as critical as the LCOS in determining post-operative prognosis. The positive effects oflevosimendan on pulmonary hypertension increase its importance in post-operative ICU management.

Kaddoura et al.,[23] in a review of the literature, suggested that in the adult population, levosimendan could be an option to facilitate successful weaning from VA-ECMO and reduce the risk of death. Current evidence shows the advantages of levosimendan in improving endothelial function, hemodynamics, and echocardiographic parameters, especially in the absence of major side effects. Although we did not encounter studies targeting the pediatric ECMO population in our literature review, we believe that levosimendan's anti-inflammatory and positive EF effects could illuminate the literature for pediatric VA-ECMO patients.

Limitations

The studies available in the literature on the effectiveness and safety of levosimendan in treating LCOS in children have several key limitations. First, many studies have small sample sizes, which makes it difficult to generalize the results to broader populations. In addition, variability in dosage regimens and treatment protocols across different studies complicates the comparison and standardization of results. The limited data on the long-term effects and potential side effects hinder a comprehensive evaluation of levosimendan's safety in pediatric patients. Furthermore, methodological differences in some studies may limit the accuracy and validity of the findings. For these reasons, larger and methodologically robust studies are needed to better understand the role of levosimendan in the treatment of pediatric LCOS.

Conclusion

Levosimendan has emerged as an effective treatment option for managing LCOS after pediatric cardiac surgery. Owing to its ability to both increase myocardial contractility and reduce systemic vascular resistance, levosimendan improves hemodynamic stability and enhances cardiac performance. While the present data suggest that levosimendan has positive effects on pediatric patients, further research is needed to assess its long-term safety and efficacy. Careful patient management and individualized dosing are essential for the successful clinical use of levosimendan. Future research will help clarify the role of this drug in pediatric LCOS treatment and contribute to the development of treatment protocols.

Disclosures

Ethics Committee Approval: The study was approved by the Liv Bona Dea Hospital Ethics Committee (no: 183, date: 01/07/2025).

Informed Consent: Informed consent was obtained from all participants.

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