Levosimendan for Postoperative Ventricular Dysfunction Following Heart Transplantation

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The development of postoperative ventricular dysfunction immediately after heart transplantation is a serious complication that leads to low-output syndrome and which necessitates circulatory support. It is one of the most common causes of early morbidity and mortality. We present our experience with 6 heart transplant patients who were treated with intravenous levosimendan, a calcium sensitizer with inodilator properties, after regular hemodynamic therapy with sympathomimetic amines failed to result in a satisfactory hemodynamic status. Use of this drug was well tolerated and brought about hemodynamic improvements that were sufficient to enable patients to be weaned from inotropic support with amines and which led to clinical recovery, with 5 of the 6 patients being discharged from the intensive care unit.

Key words: *Heart transplantation. Posttransplantation ventricular dysfunction. Inotropic agents. Levosimendan.*

Utilidad de levosimendán en la disfunción ventricular postoperatoria del injerto en el trasplante cardiaco

La disfunción ventricular del injerto en el postoperatorio inmediato del paciente trasplantado cardiaco es una complicación grave, que cursa con un síndrome de bajo gasto cardiaco y necesidad de soporte circulatorio, y es una de las causas más frecuentes de morbimortalidad inicial. Presentamos la experiencia clínica con 6 pacientes trasplantados en los que, tras un manejo hemodinámico habitual con aminas simpaticomiméticas, no se consiguió una adecuada situación hemodinámica y se utilizó levosimendán intravenoso, un fármaco sensibilizador al calcio con propiedades inodilatadoras. El uso de este fármaco fue bien tolerado y favoreció una mejoría hemodinámica que facilitó la retirada del soporte inotrópico con aminas y la recuperación clínica (con alta de UCI de 5 de los 6 pacientes).

Palabras clave: *Trasplante cardiaco. Disfunción ventricular postoperatoria del injerto. Inotropos. Levosimendán.*

INTRODUCTION

Ventricular dysfunction and its most severe manifestation, postoperative primary graft failure following cardiac transplantation in adult patients, is a serious complication that can lead to low-output syndrome, hypoperfusion, multiorgan dysfunction, and even the death of the patient. The Registry of the International Society for Heart and Lung Transplantation states that primary graft failure is the cause of up to 40% of mortality in the first 30 days postransplantation.[1] Similar figures (43%) are reported by the Spanish Registry.[2]

The hemodynamic management of these patients is complex, and the therapeutic options are restricted to pharmacological and mechanical circulatory support. Catecholamines are used and are very effective for most patients. However, they sometimes have adverse effects and on occasions are insufficient to maintain satisfactory hemodynamic status. In the most severe cases, mechanical support can be established with intraaortic balloon counterpulsation and, on rare occasions, with ventricular assist devices.[3,4] On very few occasions, and in especially selected patients, retransplantation may be an option.

Levosimendan is an inotropic vasodilator belonging to the calcium sensitizer group and has been recently introduced into clinical practice. It has proven useful in various acute cardiac failure situations, including perioperative cardiac surgery[5] and right ventricular dysfunction, by decreasing systolic pulmonary arterial pressure.[6] We present our clinical experience and outcomes in the management of 6 patients with

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TABLE 1. **Clinical Characteristics of the Patients**[a]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Female	Female	Male	Male	Male	Female
Age, y	42	33	57	54	53	51
Diagnosis	Hypertrophic cardiomyopathy	Restrictive cardiomyopathy. Amyloid negative	Ischemic dilated cardiomyopathy	Idiopathic dilated cardiomyopathy	Valvular dilated cardiomyopathy	Restrictive cardiomyopathy. Amyloidosis
NYHA functional class	IV	III	IV	IV	III	III
Urgent transplantation	No	No	Yes	No	No	No
Previous PAP, mm Hg, systolic/diastolic; average	70/48; 60	74/29; 46	39/25; 30	65/23; 40	50/29; 35	69/33; 45
Reversibility test	Not carried out	Positive (sildenafil)	Not carried out	Positive (sildenafil)	Not carried out	Not carried out
Transpulmonary gradient	12	21 baseline, 5 after drug	9	15 baseline, 5 after drug	11	15
Ischemia time, min	169	190	248	76	232	230

[a]PAP indicates pulmonary arterial pressure; reversibility test, test to measure the passive or reversible component in pulmonary pressure, carried out with sildenafil in both cases

ventricular dysfunction following heart transplantation who were treated with levosimendan after standard management.

METHODS

The study was conducted between January 2006 and April 2007 in our center, a tertiary hospital with a multidisciplinary program for cardiac transplantation and access to ventricular assist devices.

This was a descriptive prospective observational study, which analyzed levosimendan in 6 adult heart transplantation patients who developed early moderate-severe postoperative ventricular dysfunction.

All patients presented end-stage chronic heart failure with severe ventricular dysfunction and were in NYHA functional class III-IV at the time of cardiac transplantation. During the postoperative period, they developed low cardiac output syndrome compatible with early ventricular dysfunction. Hemodynamic therapy was conducted with amine administration which is the standard protocol in our unit. Levosimendan was administered when the patient presented inotropic dependency for more than 72 h, to aid in amine withdrawal or to supplement them if satisfactory hemodynamic status was not achieved (ie, cardiac indexes >2.5 L/min/m^2 and mixed venous oxygen saturation >65%). Levosimendan was not administered to patients with arterial hypotension (systolic blood pressure ≤100 mm Hg) at the time of initiating drug administration.

Previous pulmonary hypertension and ischemia times were analyzed as possible preoperative and intraoperative factors that might have an effect on the development of ventricular dysfunction in the transplanted heart. Hemodynamic response to levosimendan and the overall postoperative evolution of the patients were also studied, as well as clinical tolerance to uncover potential adverse effects attributable to the drug.

RESULTS

A total of 6 patients were studied (3 men and 3 women). Table 1 shows the baseline clinical characteristics of the patients.

All patients were in NYHA functional class III-IV prior to surgery. One patient underwent emergency transplantation due to hemodynamic deterioration that required mechanical ventilation and mechanical circulatory support with intraaortic balloon counterpulsation and pharmacological intervention with amines. Prior to transplantation, all patients presented pulmonary hypertension which was moderate-severe in 5 out of the 6 patients, with a transpulmonary gradient (TPG) ranging from 9 mm Hg to 21 mm Hg. The 2 patients with TPG >15 mm Hg responded positively to a reversibility test with sildenafil, that is, there was a significant decrease in pulmonary pressures and TPG after administering the vasodilator (Table 1).

Immediately after transplantation, all patients presented low cardiac output syndrome due to postoperative ventricular dysfunction, with cardiac indexes measured via a lung artery catheter. All patients underwent echocardiography that ruled out pericardial effusion with hemodynamic deterioration in cardiac cavities and showed predominant right ventricular dysfunction (Table 2). Pulmonary hypertension and prolonged ischemia time (248 min) may have influenced the development of right ventricular dysfunction in the only patient with mild hypertension.

All patients were treated according to our standard immunosuppression protocol, which included basiliximab (2 doses, one 4-6 h after ICU admission and a second on

TABLE 2. **Overall Postoperative Patient Evolution**[a]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Other inotropic agents combined with levosimendan	Dobutamine	Dobutamine, adrenaline	Dobutamine	No	Dobutamine, dopamine	Dobutamine, adrenaline
Withdrawal of inotropic after administering levosimendan	Yes	Yes	Yes	Levosimendan only	Yes	No
Time to withdrawal	48 h	Adrenaline 8 h; dobutamine 48 h	24 h	—	Dobutamine 12 h; dopamine 24 h	—
Other treatments, pulmonary hypertension	No	Epoprostenol, sildenafil	No	No	No	Epoprostenol, sildenafil, nitric oxide
ICU Evolution						
Respiratory insufficiency	No	No	No	No	No	Yes
Mechanical ventilation time, h	29	7	8	9	9	51 days
Acute kidney failure	No	Yes	No	No	No	Yes
Arrhythmias	Atrial rate	Node rate	No	Atrial rate	No	Fluttering
Maximum CK-MB	84	77	99	63	142	115
Other	No	Bleeding disorders	Hyperglycemia	No	Rhabdomyolysis	Multiorgan failure
Echocardiogram[b]	Dilated hypocontractile RV, normal LV	Dilated hypocontractile RV, normal LV	Biventricular insufficiency, dilated RV	Dilated hypocontractile RV, normal LV	Nondilated hypocontractile RV	Biventricular insufficiency, dilated RV
Side effects	No	No	Mild initial hypotension	No	No	Mild initial hypotension
ICU stay, d	6	6	5	4	5	51
Discharge to ward	Yes	Yes	Yes	Yes	Yes	No, death

LV indicates left ventricle; [a]RV, right ventricle
[b]Normal valvular function and absence of pericardial effusion with involvement of cardiac cavities were verified in all echocardiograms.

the fourth day posttransplantation), steroids (3 doses of 125 mg methylprednisolone, followed by prednisone at 0.5 mg/kg/12 h), mycophenolate mofetil (1-1.5 g/12 h) and cyclosporin (1-4 mg/kg/24 h). In the last patient, cyclosporin was postponed due to kidney failure immediately after transplantation.

Multiple parameters were monitored and hemodynamic management performed in all patients according to standard practice. Thus, all patients received fluids to achieve satisfactory blood volume status (until normal preload ranges were achieved), atrial epicardial pacing was performed and inotropic support provided with sympathomimetic amines. Table 3 shows the evolution of hemodynamic parameters in the 6 patients treated with levosimendan. Catecholamine administration was initiated after 72 h in 3 patients, after 96 h in 2, and 6 days after transplantation in 1 female patient.

Levosimendan was used as single inotropic agent after 72 h of dobutamine administration in patient 4 because of the need to maintain inotropic treatment due a marked decrease in cardiac output after withdrawal. The hemodynamic status improved after levosimendan infusion and the patient was discharged 24 h later. Levosimendan was administered to the remaining patients together with other inotropic drugs to optimize their hemodynamic status and to enable the withdrawal of catecholamine inotropic agents. All these patients received intravenous dobutamine infusions; 1 patient also received dopamine and 2 also received adrenaline. Similarly, to diminish post-load, pulmonary arterial vasodilators in the form of inhaled nitric oxide, epoprostenol, and sildenafil were also administered to 2 patients with pulmonary hypertension and marked predominant right ventricular dysfunction. In addition, 2 patients needed temporary mechanical support with intraaortic balloon counterpulsation (patients 3 and 6). The possibility of retransplantation was also assessed, but we finally decided against this in the light of our previous experience in similar situations, the scarce bibliographical support, and the possibility of achieving satisfactory medical management.

Levosimendan contributed to hemodynamic optimization in nearly all the patients and probably enabled them to be weaned from the other vasoactive drugs and facilitated their discharge from the unit. However, 1 patient presented torpid clinical evolution, developing multiorgan dysfunction syndrome requiring a long ICU stay and finally died. However, given the complexity of

TABLE 3. **Evolution of Hemodynamic Parameters**[a]

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Heart rate, bpm						
Before	103	120	105	110	110	115
4 h	105	120	105	110	105	115
12 h	105	120	105	110	105	110
24 h	100	120	105	110	110	110
Blood pressure, average, mm Hg						
Before	100	93	100	88	90	82
4 h	100	93	100	90	90	75
12 h	103	95	95	90	85	75
24 h	100	95	95	95	85	75
Pulmonary arterial pressure, average, mm Hg						
Before	25	28	31	20	28	38
4 h	22	28	25	20	26	32
12 h	22	28	22	18	24	32
24 h	21	28	22	16	24	30
Pulmonary capillary pressure, average, mm Hg						
Before	16	13	15	14	16	N/A
4 h	16	13	12	13	18	N/A
12 h	15	13	12	12	14	N/A
24 h	15	12	11	13	15	N/A
Central venous pressure, average, mm Hg						
Before	26	20	14	18	11	14
4 h	24	21	12	17	11	13
12 h	23	18	9	16	9	13
24 h	20	19	11	14	10	13
Cardiac index, L/min/m^2						
Before	2.47	2.05	2.3	1.72	2.1	1.81
4 h	2.58	2.7	2.7	2.22	2.3	2.3
12 h	2.63	2.59	2.9	2.88	2.51	2.24
24 h	2.68	2.49	3	2.77	2.71	2.48
Venous O_2 saturation, %						
Before	63	63	58	57	64	54
4 h	65	62	65	60	64	62
12 h	67	70	69	64	68	67
24 h	68	68	68	65	68	65

[a]N/A indicates not available.

these patients, it is understood that disease progress depends on multiple factors.

An initial bolus of levosimendan (12 µg/kg) was administered to the first 4 patients, whereas the other 2 patients did not receive a loading dose. After the initial bolus, continuous intravenous perfusion was started at 0.1 µg/kg/min, and was increased up to 0.15 µg/kg/min in 3 patients. It is worth highlighting that levosimendan was well tolerated by all patients. The only adverse effect observed was a slight reduction in blood pressure in 2 patients at the beginning of treatment, which did not require the dose to be adjusted.

Table 2 shows the overall postoperative evolution of patients during their ICU stay. Attention should be drawn to the clinical improvement obtained with the hemodynamic support provided, which enabled the withdrawal of inotropic agents and all the patients to be discharged from the ICU after 4-6 days except for the patient who suffered multiorgan dysfunction syndrome and died.

DISCUSSION

Orthotopic cardiac transplantation is an effective treatment in selected patients with terminal heart failure.[7] Despite the advances in patient management before, during and after heart transplantation, postoperative ventricular dysfunction and its main manifestation, primary graft failure, continues to be a potentially severe complication following this intervention, associated with worse prognosis and early mortality in a high percentage of patients.[1,2] Factors contributing to the development of acute cardiac allograft rejection include inadequate preservation of the organ, prolonged ischemia time, myocardial stunning secondary to ischemia-reperfusion, cellular or humoral rejection, donor-dependent factors (such as female sex,

weight mismatch between the donor and recipient, reduced contractility associated with brain death, or myocardial contusion) and some recipient-dependent factors, mainly preexisting pulmonary hypertension and baseline ischemic or valvular etiology.[8-11]

The management of patients with ventricular dysfunction normally involves pharmacological intervention for circulatory support (catecholamines and phosphodiesterase inhibitors) and, on some occasions, mechanical support with intraaortic balloon counterpulsation or ventricular assist devices.

In recent years, levosimendan, an inotropic vasodilator, has been included in the pharmacological arsenal. This drug increases the sensitivity of contractile proteins in myofilaments to calcium via its direct action on troponin C. This increases myocardial contractility without increasing the amount of intracellular calcium and, as a result, without increasing myocardial oxygen consumption (unlike catecholamines). In addition, levosimendan stimulates the adenosine triphosphate-dependent potassium channels, which leads to arterial and venous vasodilatation and decreases afterload.[12,13] Other effects attributed to this drug include phosphodiesterase III inhibition at high doses, antistunning effects in post-ischemic myocardium,[14,15] and myocyte apoptosis inhibition.[16]

Numerous clinical trials with high numbers of patients have been conducted with levosimendan. These studies confirm the efficacy and safety of levosimendan in the context of acute heart failure of multiple origin.[17-20] The characteristics of this drug and the clinical results obtained from these studies have led the European Society of Cardiology to consider levosimendan as a therapeutic option in patients with heart failure with symptomatic low output secondary to systolic heart failure without severe arterial hypotension. This is a class IIa recommendation with a level of evidence B.[21] The search for potential uses of levosimendan in different clinical situations involving ventricular dysfunction or low cardiac output has led to numerous studies being conducted in the context of acute decompensation episodes in chronic heart failure and in acute heart failure of different etiology, such as postoperative heart surgery, cardiogenic shock, and even ventricular dysfunction in septic shock.[22-26]

Given that levosimendan combines pulmonary vasodilating properties and inotropic action, it has also been used in patients with right ventricular dysfunction,[5] in the diagnosis of a potential reversible component in increased pulmonary vascular resistance, to predict post-transplantation cardiac performance[27] and even in isolated cases of graft failure after heart transplantation.[28,29]

This article analyzes our clinical experience in the use of levosimendan in a series of patients with ventricular dysfunction in the immediate period after cardiac transplantation. Although our study deals with a small number of patients, it is the largest series published. It should be noted that levosimendan is well-tolerated, without serious adverse effects, and contributed to hemodynamic improvement in both the one patient who received it as the only inotropic administered (after stopping dobutamine) and in the remaining patients, except in the one who presented multiorgan failure. Similarly, it is very likely that it enabled amine withdrawal, but understood as a contributing factor in a complex situation where multiple factors play a role.

Therefore, we conclude that this new inotropic vasodilator, a calcium sensitizer, has a good safety profile and improves hemodynamic status in this subgroup of patients who are characterized by low cardiac output with predominant right ventricular dysfunction and relatively high pulmonary hypertension.

Nevertheless, this study is quite small and cannot provide solid recommendations; rather, it should be viewed as a seed to encourage setting up a multicenter study with a large number of patients capable of establishing suitable indications and guidelines for the use of levosimendan, as well as the profile of patients who would benefit most from its use.

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