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Cardiac Pharmacology

Effects of Levosimendan on Systemic Perfusion in Patients with Low Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Score: Experience from a Single Center in Taiwan

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Background: Patients with cardiogenic shock have a high risk of mortality. Intravenous levosimendan can provide pharmacologic inotrope support.

Objectives: We aimed to investigate the effect of levosimendan in patients with extremely severe cardiogenic shock and low Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score with or without mechanical circulatory support.

Methods: From January 2017 to May 2019, 24 patients with INTERMACS 1-4 were enrolled in this retrospective study. All patients had systemic malperfusion and were treated with levosimendan. Biochemistry data related to systemic perfusion were recorded and compared before and at 24 and 72 hours after levosimendan administration. Echocardiography and Kansas City Cardiomyopathy Questionnaire (KCCQ) were completed 2 months later to assess left ventricular ejection fraction (LVEF) and quality of life (QoL), respectively.

Results: Arterial pressure and heart rate did not significantly differ before and after levosimendan administration. Atrial fibrillation and ventricular premature complex increased without significance. The dose of inotropes could be significantly tapered down. There were no significant differences in blood urea nitrogen, creatinine, and lactate levels. Urine output significantly increased ($p = 0.018$), and liver-related enzymes improved but without significance. B-type natriuretic peptide significantly decreased ($p = 0.007$) at 24 hours after levosimendan administration. Echocardiography showed significantly improved LVEF 2 months later ($22.43 \pm 8.13\%$ to $35.87 \pm 13.4\%$, $p = 0.001$). KCCQ showed significantly improved physical activity and greater relief of symptoms ($p = 0.003$). The survival-to-discharge rate was 75%.

Conclusions: We observed a decrease in B-type natriuretic peptide, better urine output, and alleviated hepatic injury in the levosimendan group. Most patients who survived without transplantation had significantly improved LVEF and better QoL after levosimendan administration.

Key Words: Cardiogenic shock • End-stage heart failure • Levosimendan • Systemic perfusion

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INTRODUCTION

Cardiogenic shock is an emergency hemodynamic instability and often results in irreversible vital organ damage despite immediate resuscitative treatment. The overall in-hospital mortality rate of cardiogenic shock has been reported to be 39%, ranging from 27%

to 51%.[1] Moreover, the mortality rate may increase up to 70%-90% if aggressive and highly experienced technical care is not performed.[2] Therefore, inotropes are usually widely administered immediately, and even so, some of these patients need mechanical circulatory support (MCS) to stabilize their hemodynamic condition and maintain normal perfusion of the visceral organs. In these patients, MCS plays an important role in organ preservation, and is viewed as a bridge to recovery, heart transplantation, or durable permanent ventricular assist device (VAD). Levosimendan is a drug that acts as a calcium sensitizer[3,4] and as an opener of adenosine triphosphate-sensitive potassium channels.[5] Recently, levosimendan has been evaluated extensively for the treatment of acute decompensated heart failure and applied in a range of other settings characterized by impaired cardiac performance, including patients with cardiac surgery,[6] cardiogenic shock, and low cardiac output.[7-10] However, the effectiveness of levosimendan is uncertain for patients with a low Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score (≤ 4), especially INTERMACS 1 and 2 for whom systemic malperfusion has developed and MCS might be indicated. Thus, we conducted this study to investigate the effects of levosimendan in patients with INTERMACS 1-4.

MATERIALS AND METHODS

Patient population and data collection

This retrospective study enrolled 24 patients (18 men and 6 women; Figure 1) with acute heart failure and organ dysfunction despite inotrope usage who were admitted from January 2017 to May 2019 at our institution. The study protocol was approved by our institution's ethics committee (TSGHIRB number A202005034). Table 1 presents the patients' characteristics. The mean age was 65.83 ± 5.88 years, the mean weight was 64.54 ± 4.69 kg, and the mean body mass index was 24.13 ± 1.29 kg/m^2. Regarding systemic diseases, seven patients had type 2 diabetes mellitus (29.2%), nine had hypertension (37.5%), eight had hyperlipidemia (33.3%), 15 had a history of coronary artery disease (62.5%), 11 had a valve disease (45.8%), and 17 had atrial fibrillation (70.8%). All patients suffered from either decompensated heart failure with cardiogenic shock, defined as INTERMACS 1-2, or end-organ malperfusion, defined as INTERMACS 3-4. Three had undergone cardiopulmonary resuscitation (CPR) and received MCS initially, including intra-aortic balloon pumping (IABP) in one patient and extracorporeal membrane oxygenation (ECMO) in two patients. The etiology of cardiogenic shock included dilated cardiomyopathy, ischemic cardiomyopathy, and postcardiotomy syndrome. All patients had renal insuf-

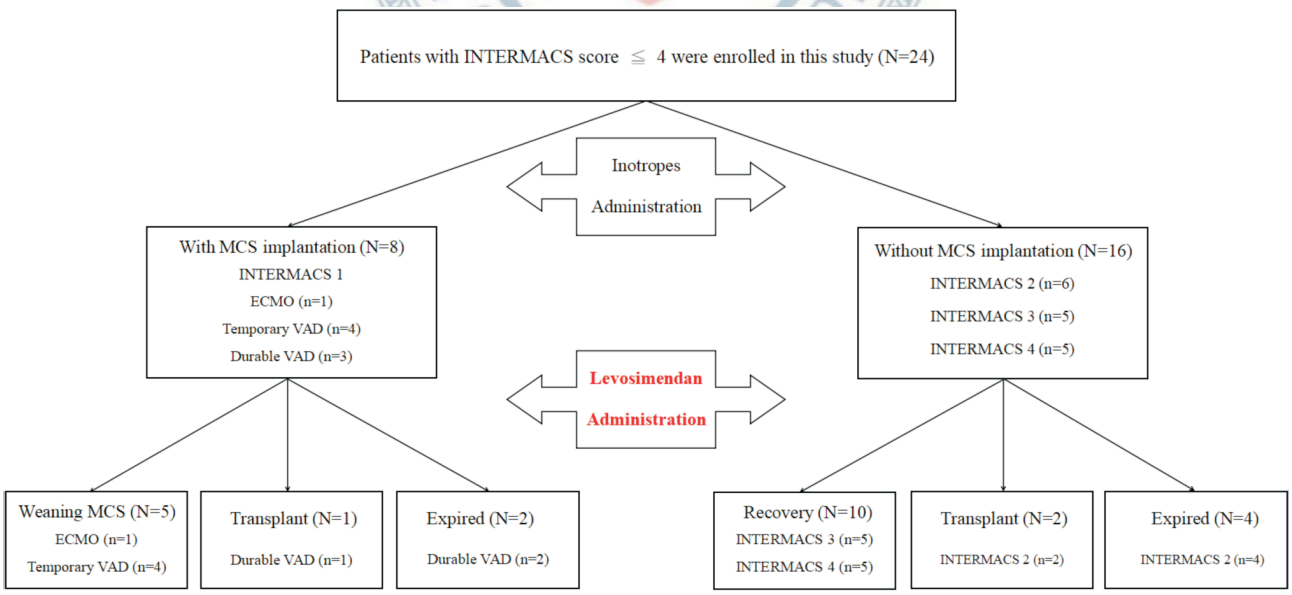


Figure 1. *The algorithm of patients enrolled in this study. ECMO, extracorporeal membrane oxygenation; INTERMACS score, Interagency Registry for Mechanically Assisted Circulatory Support score; VAD, ventricular assist device.*

Table 1. Study group demographic data

	Mean ± SD
Age (yr)	65.8 ± 5.9
Male, n (%)	18 (75)
Weight (kg)	64.5 ± 4.7
BMI (kg/m^2)	24.1 ± 1.3
Underlying disease	
Diabetes, n (%)	7 (29.2)
Hypertension, n (%)	9 (37.5)
Hyperlipidemia, n (%)	8 (33.3)
CAD, n (%)	15 (62.5)
Valve disease, n (%)	11 (45.8)
Atrial fibrillation, n (%)	17 (70.8)
Medication	
Dapagliflozin, n (%)	7 (29.2)
Ivabradine, n (%)	20 (83.3)
Atorvastatin, n (%)	8 (33.3)
Eplerenone, n (%)	22 (91.7)
Sacubitril + Valsartan, n (%)	22 (91.7)
Cause	
DCM, n (%)	14 (58.3)
ICM, n (%)	7 (29.2)
Postcardiotomy syndrome, n (%)	3 (12.5)
INTERMACS score	
1, n (%)	8 (33.3)
2, n (%)	6 (25.0)
3, n (%)	5 (20.8)
4, n (%)	5 (20.8)
CPR	
CPR-IABP, n (%)	1 (4.2)
CPR-ECMO, n (%)	2 (8.3)
Mechanical Device	
IABP, n (%)	1 (4.2)
ECMO, n (%)	6 (25)
VAD, n (%)	7 (29.2)

BMI, body mass index; CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; ICM, ischemic cardiomyopathy; INTERMACS, low Interagency Registry for Mechanically Assisted Circulatory Support; VAD, ventricular assist device.

ficiency, with either a decreased 24-hour urine output (1360 ± 385.4 mL/day) or abnormal renal function, including blood urea nitrogen (BUN) level of 51.3 ± 9.2 mg/dL and creatinine (Cr) level of 2.2 ± 0.5 mmol/L. All patients also had abnormal liver-related enzyme levels, including a glutamic oxaloacetic transaminase (GOT) level of 70.8 ± 56.5 U/L, glutamic pyruvic transaminase (GPT) level of 65.0 ± 50.7 U/L, and total bilirubin level of 1.7 ± 0.8 mg/dL. All patients had lactate acidosis resulting from cardiogenic shock, with a serum lactate level of 3.0 ± 1.7 mmol/L and bicarbonate level of 21.8 ± 1.6 mmol/L. Twelve patients needed intubation with ventilator support, and the PaO2/FiO2 ratio was maintained within 200-300 mmHg. Echocardiography revealed impaired systolic function with left ventricular ejection fraction (LVEF) of 26.1 ± 2.8%, ventricular remodeling with left ventricular end-diastolic diameter (LVEDD) of 61.1 ± 2.0 mm, left ventricular end-systolic diameter (LVESD) of 51.5 ± 2.3 mm, and pulmonary hypertension with pulmonary artery pressure (PAP) of 41.6 ± 2.8 mmHg. All patients received inotropes, including dopamine, dobutamine, and norepinephrine to maintain hemodynamics. Most patients were diagnosed with chronic congestive heart failure and had optimal medical medications, including beta-blockers, diuretics, sacubitril/valsartan, and ivabradine, if not contraindicated. MCS was applied if low cardiac output exacerbated despite the use of these medications. The low cardiac output syndromes included low mean arterial pressure, acute pulmonary edema, oligouria, congestive liver, and conscious disturbance. In patients who receive CPR, peripheral ECMO would increase cardiac afterload.[11] Usually the left ventricle is still akinesic and in distension, which would exacerbate pulmonary edema. This is the indication for VAD intervention from ECMO or IABP. Therefore, all three CPR patients initially treated with IABP or ECMO were bridged to VAD with temporary Levitronix® CentriMag (Levitronix®, Waltham, MA, USA). Another five patients received emergency MCS, including VAD in four patients and ECMO in one patient (Figure 1). These eight patients with MCS had an INTERMACS score of 1 (33%). Meanwhile, six had an INTERMACS score of 2 (25%), five had an INTERMACS score of 3 (20.8%), and five had an INTERMACS score of 4 (20.8%). All patients were monitored in the intensive care unit and received levosimendan at this point (20-minute intravenous bolus infusion at 6-12 mcg/kg followed by a continuous 24-hour infusion of 0.1 mcg/kg/min). In the patients with MCS, levosimendan was administered immediately after MCS implantation and drip for 24 hours. The common side effects, such as vasodilation-related hypotension and ventricular arrhythmia, were closely monitored and recorded. We discontinued levosimendan if frequent ventricular premature beat (VPC) was present or if profound hypotension exacerbated, which did not respond to vasopressors.

Eventually, all 24 patients completed the levosimendan treatment.

Inotrope adjustment, hemodynamic status, and systemic perfusion monitoring

Dopamine was always our first-line inotrope because of its beneficial effect in increasing cardiac output and systemic vascular resistance.[12] Our second inotrope was dobutamine or norepinephrine, depending on the patients' cardiac rhythm and vascular resistance. Dobutamine was prescribed to increase the cardiac output solely without increasing the afterload,[13] and norepinephrine was used in patients with decreased peripheral systemic resistance lower than 800 dyn·s·cm^{-5} measured using a Swan-Ganz catheter.[14] As long as the MAP could be maintained within 70-100 mmHg and low cardiac output subsided, the inotropes were tapered to the minimum dose as quickly as possible. Regarding systemic perfusion, we monitored variations in systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP at baseline, 24 hours after levosimendan administration, and 72 hours after levosimendan administration. We recorded and compared the daily urine output as well as BUN/Cr, lactate, GOT, GPT, and total bilirubin levels. Diuretic agents, such as eplerenone and furosemide, were prescribed in all cases to maintain a urine output of > 0.5 mL/kg/hour. Eventually, two cases had cardiorenal syndrome and received continuous venovenous hemofiltration during levosimendan administration. These cases were excluded from the 24-hour urine output measurement. Regarding the laboratory data for the cardiac system, we compared troponin I (Tro-I) and B-type natriuretic peptide (BNP) levels at baseline, 24 hours after levosimendan administration, and 72 hours after levosimendan administration. During weaning from ECMO and temporary VAD, daily bedside echocardiography was performed to assess the recovery of heart function. The weaning criteria included pump flow of < 1.0 l/min, total inotrope dose of < 5 μg/kg/min, good end-organ perfusion, absence of pulmonary congestion, and stable hemodynamic status. The ECMO period was usually < 7 days.

Measurement of cardiac system and quality of life (QoL)

Transthoracic echocardiography was performed at 2 months after levosimendan treatment. We focused on LVEF, PAP, LVESD, and LVEDD. Regarding the evaluation of QoL, we used the Kansas City Cardiomyopathy Questionnaire (KCCQ) to assess the individual's cognition of heart failure status.[15] The KCCQ Qualification includes symptom, physical limitation, social limitation, and QoL domains and the overall summary score. Transthoracic echocardiography and KCCQ Qualification were both completed before levosimendan treatment and at 2 months after levosimendan treatment. Patients who underwent transplantation or died within 2 months after levosimendan treatment were excluded from the 2-month measurements.

Statistical analysis

We analyzed the patients' characteristics, laboratory data, and cardiac function and compared the differences in data between those obtained at baseline, 24 hours after levosimendan administration, and 72 hours after levosimendan administration. The differences in echocardiographic and KCCQ Qualification data obtained at baseline and at 2 months after levosimendan treatment were also examined.

SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all analyses. Continuous variables (transthoracic echocardiographic and KCCQ Qualification data) were reported as means ± standard deviation and compared using the unpaired t-test with post hoc test. For the multivariate analysis of repetitive measures, repeated measure ANOVA was used to compare the differences in laboratory data, inotrope use, and hemodynamic status obtained in each patient at various time points. A p-value < 0.05 was considered to be statistically significant.

RESULTS

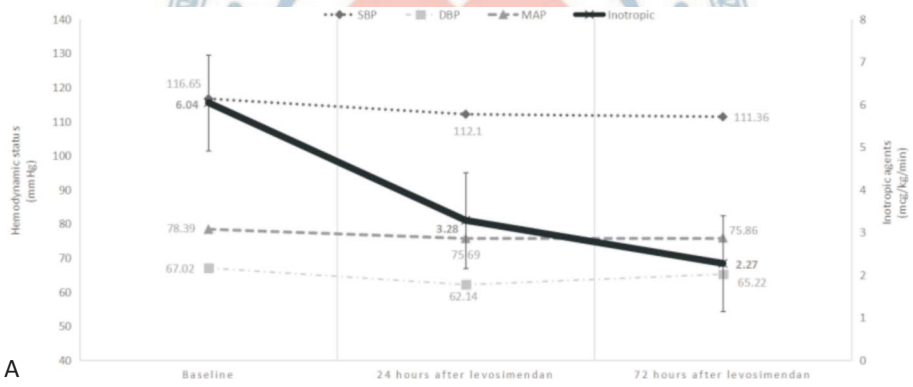
Inotrope adjustment, hemodynamic status, and systemic perfusion monitoring

Comparing the hemodynamic status before and after levosimendan administration (Table 2), there were no significant changes in SBP, DBP, MAP, and heart rate. However, the total dosage of inotropes was significantly tapered down (p = 0.024) (Figure 2), although no significant difference was noted in each inotrope. With regards to the rhythm variation at 24 hours after levosimendan

Table 2. Inotropes and hemodynamic status variation

	Baseline Mean ± SD	24 hours after levosimendan Mean ± SD	72 hours after levosimendan Mean ± SD	p value
Inotropes				
Total dosage	6.04 ± 3.06	3.28 ± 1.38	2.27 ± 1.16	0.024*
Dopamin (mcg/kg/min)	3.62 ± 1.25	2.59 ± 1.39	1.81 ± 1.10	0.104
Norepinephrine (mcg/kg/min)	6.69 ± 13.94	3.32 ± 3.70	1.64 ± 4.56	0.516
Dobutamine (mcg/kg/min)	3.88 ± 2.63	1.93 ± 2.24	0.98 ± 1.59	0.080
Hemodynamic status				
Systolic BP (mmHg)	116.65 ± 9.04	112.1 ± 8.77	111.36 ± 7.48	0.612
Diastolic BP (mmHg)	67.02 ± 5.43	62.14 ± 6.25	65.22 ± 5.84	0.447
Mean arterial pressure (mmHg)	78.39 ± 5.46	75.69 ± 5.26	75.86 ± 5.37	0.697
Heart rate (beat per minute)	87.27 ± 5.35	86.98 ± 6.10	95.92 ± 7.38	0.075
Rhythm				
Sinus, n (%)	13 (54.2)	8 (33.3)	9 (37.5)	
Atrial fibrillation, n (%)	7 (29.2)	11 (45.8)	9 (37.5)	
VPC, n (%)	3 (12.5)	4 (16.7)	5 (20.8)	
AV block, n (%)	1 (4.2)	1 (4.2)	1 (4.2)	

AV block, atrioventricular block; BP, blood pressure; SD, standard deviation; VPC, ventricular premature beat.
* Compared with baseline, p < 0.05.



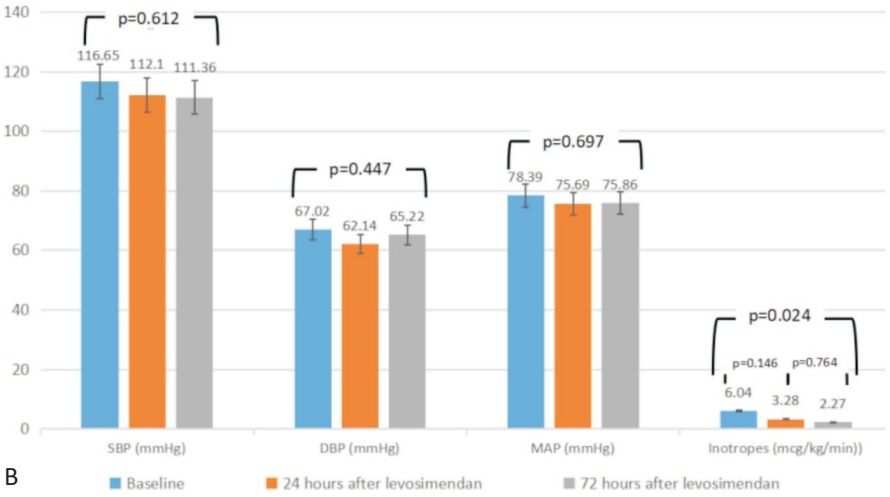


Figure 2. *(A) Mean with standard deviation bars of inotrope variation and mean hemodynamic status between data obtained at baseline, 24 hours after levosimendan administration, and 72 hours after levosimendan administration are presented in a line chart. The total inotrope dosage could be tapered down without hemodynamic compromise. (B) p-value of mean with standard deviation bars hemodynamic status and inotrope variation between data obtained at baseline, 24 hours after levosimendan administration, and 72 hours after levosimendan administration in the analysis of variance and post hoc test.*

administration, four (16.6%) patients had new-onset atrial fibrillation, and one (4.1%) had new-onset VPC. At 72 hours after levosimendan administration, two (8.3%) patients had new-onset VPC. No malignant ventricular rhythm was recorded in any of the patients within 72 hours after levosimendan administration.

Regarding systemic organ perfusion (Table 3), the daily urine output increased significantly (1360 ± 385.4 mL at baseline versus 2142.4 ± 429.8 mL at 72 hours after levosimendan administration, p = 0.018) although there were no significant differences in the serum levels of BUN or Cr. Liver function tests, including GOT, GPT, and total bilirubin, improved, although the p-value was not statistically significant. The serum lactate level decreased without statistical significance.

Regarding the cardiac laboratory data, the BNP level significantly decreased (4197.7 ± 1001.0 pg/mL at baseline versus 2462.8 ± 623.5 pg/mL at 72 hours after levosimendan administration, p = 0.007). There was no significant difference in the cardiac enzyme Tro-I (p = 0.801).

Cardiac system and QoL

Regarding the echocardiographic parameters (Table 4), LVEF showed a statistically significant improvement (22.4 ± 8.1% to 35.9 ± 13.4%, p = 0.001). Both LVESD and LVEDD also decreased (53.5 ± 9.3 to 44.3 ± 16.4 mm, p = 0.063 and 62.6 ± 8.6 to 55.1 ± 12.0 mm, p = 0.037, respectively). These parameters indicated that the cardiac remodeling had improved. PAP showed a statistically significant reduction (42.0 ± 14.1 to 32.5 ± 11.4 mmHg, p = 0.039), and BNP level showed a reduction, although without statistical significance (3,434.3 ± 2,117.4 to 2,552.6 ± 1,858.8 pg/ml, p = 0.206). Regarding the QoL, the KCCQ Qualification showed a significant improvement in physical activity and social limitation (p = 0.011 and 0.016, respectively). In addition, the symptoms were relieved and the QoL significantly improved (p < 0.001).

Among the eight patients with MCS, five were successfully bridged to recovery, including four from temporary VAD and one from ECMO. One patient with durable VAD was eventually bridged to heart transplantation, and the other two died of multiple organ failure. Among the 16 patients without MCS, 10 INTERMACS 3 and 4 patients had an uneventful recovery to discharge. Among the INTERMACS 2 patients, two were bridged to transplantation, and four died of profound cardiogenic shock (Figure 1).

DISCUSSION

Levosimendan is a calcium sensitizer that increases myocardial contractility and cardiac output without increasing intracellular calcium concentrations and oxygen demand.[16,17] Cardiogenic shock always results in multiple organ dysfunction and eventually death. Many

Table 3. Systemic organ variation

	Baseline Mean ± SD	24 hours after levosimendan Mean ± SD	72 hours after levosimendan Mean ± SD	p value
pH of ABG	7.444 ± 0.02	7.432 ± 0.04	7.457 ± 0.02	0.436
HCO3	21.84 ± 1.60	22.36 ± 2.12	21.64 ± 2.93	0.880
Lactate (mmol/L)	2.95 ± 1.66	2.37 ± 0.77	2.03 ± 0.89	0.559
BUN (mg/dL)	51.25 ± 9.2	49.13 ± 12.5	44.83 ± 11.4	0.690
Serum creatinine (mg/dL)	2.22 ± 0.54	1.87 ± 0.46	1.77 ± 0.50	0.391
Urine output (ml/24 hr)	1360 ± 385.4	1819.6 ± 359.5	2142.4 ± 429.8	0.018*
GOT (U/L)	70.75 ± 56.48	41.42 ± 15.1	40.83 ± 16.09	0.365
GPT (U/L)	64.96 ± 50.69	42.96 ± 22.99	30.88 ± 11.55	0.312
Total bilirubin (mg/dL)	1.72 ± 0.83	1.82 ± 1.08	1.46 ± 0.79	0.837
TroI (ng/ml)	1.898 ± 2.50	0.796 ± 0.75	1.388 ± 1.94	0.801
BNP (pg/ml)	4197.67 ± 1000.97	2955.79 ± 714.07	2462.83 ± 623.46	0.007*

ABG, arterial blood gas; BNP, B-type natriuretic peptides; BUN, blood urea nitrogen; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HCO3, bicarbonate; SD, standard deviation; TroI, troponin I.
* Compared with baseline, p < 0.05.

Table 4. Two-month follow up, excluding patients who were expired and underwent transplantation

	Before levosimendan (N = 15) Mean ± SD	Two-month after levosimendan (N = 15) Mean ± SD	Difference p value
Echocardiography			
LVEF (%)	22.43 ± 8.13	35.87 ± 13.4	0.001
PAP (mmHg)	41.95 ± 14.1	32.47 ± 11.4	0.039
LVESD (mm)	53.52 ± 9.33	44.27 ± 16.4	0.063
LVEDD (mm)	62.57 ± 8.61	55.13 ± 12.0	0.037
KCCQ qualification			
Physical limitation	35.85 ± 6.03	41.17 ± 6.14	0.011
Symptoms	35.91 ± 6.92	46.17 ± 8.58	0.000
Quality of life	35.95 ± 7.22	47.17 ± 8.56	0.000
Social limitation	35.60 ± 7.22	41.56 ± 7.26	0.016
Overall summary	36.10 ± 6.68	43.44 ± 7.29	0.003
Cardiac enzyme			
BNP (pg/ml)	3434.3 ± 2117.4	2552.6 ± 1858.8	0.206
Medication			
Dapagliflozin, n (%)	4 (26.7)	3 (20)	
Ivabradine, n (%)	13 (86.7)	12 (80)	
Atorvastatin, n (%)	4 (26.7)	4 (26.7)	
Eplerenone, n (%)	14 (93.3)	13 (86.7)	
Sacubitril + Valsartan, n (%)	13 (86.7)	11 (73.3)	

BNP, B-type natriuretic peptides; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PAP, pulmonary artery pressures; SD, standard deviation.

studies and meta-analysis have emphasized that levosimendan is more effective in low-cardiac-output patients without cardiogenic shock than in patients with cardiogenic shock.[18] Moreover, patients with shock with a low INTERMACS (≤ 4) score are usually indicated for MCS to maintain systemic perfusion. The application of levosimendan was seldom been reported in this critical group, especially for temporary VAD. Theiss et al. reported the preconditioning benefit of levosimendan in patients with right heart insufficiency prior to LVAD implantation.[19] At our institute, we use the INTERMACS score to decide the application of MCS when optimal medication treatment fails (Figure 1). In our series, eight patients had an INTERMACS score of 1 and underwent MCS placement because of life-threatening hypotension and critical organ hypoperfusion. In this MCS group, levosimendan played an important role in weaning from MCS. One patient was weaned from ECMO and four patients were weaned from temporary VAD (Levitronix®, Waltham, MA). Usually, the ECMO weaning rate in Taiwan is approximately only 30% in patients with cardiogenic shock,[20] and the weaning rate from Levitronix® CentriMag VAD ranges from 30% to 40%.[21-23] At our heart center, the weaning rates from ECMO and temporary VAD were 38% and 45%, respectively. Therefore, weaning from MCS in these patients should be done very carefully because of the high failure rate. If ECMO weaning is impossible, the patient should be advanced to either transplantation or self-paid intracorporeal VAD. The acceptable duration of temporary Levitronix® CentriMag is usually < 1 month, which provides more time to wait for a heart donation. Cardiac transplantations are limited both in Taiwan and also worldwide owing to a donor shortage. Durable intracorporeal VADs, such as HeartMate3 or HeartWare, have been conditionally approved by the Taiwan National Health Insurance Bureau since 2018. Therefore, ECMO and Levitronix® CentriMag VAD have become the major types of MCS for cardiogenic shock in Taiwan. Levosimendan might play an important role in weaning patients from MCS. In our data, levosimendan remarkably improved cardiac performance, maintained hemodynamics, and reduced the total dosage of inotropes (Figure 2). Conventional inotropes provide limited help in these critical patients.[18] In our analysis, the levosimendan group had a better weaning rate from MCS, including ECMO and temporary VAD. Further-

more, the levosimendan group had a shorter duration of MCS, if weaning was possible. It is well known that MCS, especially VAD, can provide absolute hemodynamic support, and it is the mainstream treatment for cardiogenic shock.[24,25] However, MCS is also associated with lethal complications such as systemic embolism or coagulopathy.[26-28] Therefore, a shorter MCS duration implies fewer complications. Further studies with more cases should be conducted to analyze the impact and benefit of levosimendan among patients with various types of MCS.

Cardiogenic shock patients without MCS often receive large doses of inotropes, causing vessel constriction. This is a vicious cycle for the decompensated heart because of the persistently high afterload and worse perfusion resulting from vessel constriction. Previous studies have reported that long-term inotrope use may result in inotropic dependency and increased mortality rate.[13,29] Levosimendan acts as both an inotrope and vessel dilator, which is referred to as an inodilator.[30] In our results, the dosage of inotropes could be tapered down while maintaining a stable hemodynamic status (Figure 2). Three-quarters of the patients in our series had an uneventful recovery or underwent heart transplantation in a stable condition. Fang et al.[18] reported a mortality rate of patients with cardiogenic shock treated with levosimendan of 29.7%-36.3% at 1-year follow-up. They did not include patients with New York Heart Association Functional Classification of IV. To present the severity of their condition before levosimendan treatment, we categorized our patients according to the INTERMACS score, which is frequently applied to classify these extremely critical patients for MCS. Although three of our patients were indicated for transplantation, our 1-year survival rate was 75% (Figure 1), which is much better compared to the results of previous studies. With regards to its effect in organ preservation, levosimendan has been proven to not cause kidney or liver ischemia-reperfusion injury and to preserve organ function in animal trials since 2012.[31,32] In a human study, Avgeropoulou et al. also showed that levosimendan could reduce oxidative markers and increase the antioxidant system,[33] although increased reactive oxygen species production by a failing heart may result in cardiac contractile dysfunction and ischemia-reperfusion injury.[34-36] In the Levosimendan Compared with Dobutamine in Severe Low-Output Heart Failure study, the authors reported that levosimendan could reduce the serum Cr level by > 0.5 mg/dL in > 50% patients, whereas only 10% of patients without levosimendan treatment showed a reduction in serum Cr level.[8] In our patients with severe conditions, the Cr level was reduced by a mean of 0.45 mg/dL, and the daily urine output significantly improved at 72 hours after levosimendan administration. Although levosimendan has been reported to not cause liver ischemia-reperfusion injury in anesthetized rats,[31] few human trials have shown hepatic benefits with levosimendan treatment in patients with decompensated heart failure. Although not significant, we observed a trend toward improved hepatic function after levosimendan treatment. In our study, the lactate level was reduction by a mean of 0.92 mmol/L, but without statistical significance. Taken together, we observed that renal and hepatic performances were better in the levosimendan group. Based on previous studies, it is possible that this is due to opening of the microcirculation.

Levosimendan has been reported to alleviate pulmonary congestion.[37-40] In the LevoRep study, Altenberger et al.[41] reported that 31.7% of their patients showed ≥ 20% improvement in the 6-minute walk test, and that 46% of their patients showed ≥ 15% improvement in the KCCQ after 2 months of follow-up. Our study revealed improvements in symptoms in 26.6% of the patients, physical limitation in 11.4%, and overall summary score in 17.6% (Table 4). Slawsky et al. reported that levosimendan improved many hemodynamic parameters, including pulmonary capillary wedge pressure, pulmonary artery pressure, MAP, systemic vascular resistance, and pulmonary vascular resistance, within 24 hours after its administration.[42] We also showed an improvement in LVEF and PAP reduction by echocardiography, and even a reversal of ventricular remodeling in this extremely critical population (Table 4). Nieminen et al. and Ortis et al. reported that levosimendan had both hemodynamic and neurohumoral effects to reduce BNP level, which might synergically contribute to the relief of symptoms and improvement in QoL.[44,45] Our findings of decreased BNP level and low mortality rate are consistent with previous studies.

Study limitations

The main limitation of this study is the small size of

the population. Further studies are necessary to observe and prove the long-term effects of levosimendan. Second, this is a retrospective study, and no comparison with an objective control group was performed. It is relatively difficult to conduct a prospective randomized trial among these critically ill patients.

CONCLUSIONS

We observed a trend toward better system perfusion in patients with a low INTERMACS score in the levosimendan group. Furthermore, levosimendan may potentially help in weaning from MCS, including ECMO and temporary VAD. Nevertheless, further studies with adequate control groups are required to prove its efficacy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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