J Med Sci 2023;43 (4):167-176
DOI: 10.4103/jmedsci.jmedsci_209_22

ORIGINAL ARTICLE

Levosimendan as Adjuvant Therapy for Cardiogenic Shock Patients with Temporary Ventricular Assist Device

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Background: Temporary ventricular-assisted device (VAD) provides timely organ perfusion in patients with cardiogenic shock and serves as a bridge to heart transplant. Intravenous levosimendan could provide pharmacologic inotropic support. **Aim:** We aimed to investigate the adjuvant efficacy of levosimendan in patients with temporary VAD, especially for VAD weaning. **Methods:** We retrospectively reviewed the medical records of patients receiving temporary VAD for cardiogenic shock between January 2017 and May 2019 in a medical center in Taiwan. Patients were divided into the levosimendan (n = 9, administered levosimendan immediately after VAD), and control groups (n = 20, no levosimendan administered). The biochemistry of systemic perfusion was compared at 1 and 3 days after VAD. After 2 months, the cardiac function of the patients with successful VAD weaning was evaluated by echocardiography. At 6 months follow-up, survival outcome and Kaplan–Meier survival curves were presented. **Results:** In total, 29 patients receiving temporary VAD for cardiogenic shock were enrolled, including 9 patients treated with levosimendan infusion. In the levosimendan group, both mean arterial pressure and lactate level decreased significantly (P = 0.037 and 0.023, respectively), and the ratio of arterial oxygen partial pressure to fractional inspired oxygen improved significantly (P = 0.048). No difference in inotropes tapering, consciousness, systemic perfusion biochemistry, and cardiac enzymes. Echocardiography showed significantly improved systolic function and pulmonary artery pressure 2 months later (P = 0.043 and 0.046, respectively) in patients with successful weaning. The levosimendan group had a better weaning rate (P = 0.013) and lower mortality rate (P = 0.571) at 6-month follow-up. **Conclusion:** The levosimendan group showed a better weaning rate and lower mortality rate.

Key words: Cardiogenic shock, end-stage heart failure, levosimendan, organ malperfusion, ventricular-assisted device

INTRODUCTION

Cardiogenic shock is an emergent hemodynamic instability and always results into irreversible vital organ damage if resuscitative treatment was not performed immediately. In literature, the overall in-hospital mortality rate of cardiogenic shock is reported as 39%, ranging from 27% to 51%.[1] Moreover, the mortality rates may increase up to 70%–90% if aggressive and highly experienced technical care is not performed.[2] In the past three decades, temporary ventricular-assisted device (VAD) was reported to provide optimal organ perfusion for cardiogenic shock and become a bridge to heart transplantation.[3] However, the shortage of heart donors always results in prolonged VAD placement, which may cause complications such as coagulopathy, infection, hemolysis, and catastrophic thrombus event.[4] In the real world, actually, more than half of patients were reported having short-term VAD support for more than 1 month.[5] Hence, VAD weaning

Received: September 30, 2022; Revised: October 05, 2022; Accepted: October 06, 2022; Published: October 29, 2022
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How to cite this article: Wang YH, Hsu PS, Tsai YT, Lin CY, Ke HY, Tsai CS. Levosimendan as adjuvant therapy for cardiogenic shock patients with temporary ventricular assist device. J Med Sci 2023;43:167-76.

becomes a concern issue, especially when durable VAD or heart transplant is not practicable temporarily.

Levosimendan is a drug that acts as a calcium sensitizer[6-8] and as the opener of adenosine triphosphate-sensitive potassium (K-ATP) channels. [9] Recently, levosimendan had been evaluated extensively for the treatment of acute decompensated heart failure and also applied in a range of other settings characterized by impaired cardiac performance, including patients undergoing cardiac surgery, [10] cardiogenic shock, and low cardiac output. [11-13] However, levosimendan was few reported to be applied as an adjuvant therapy in patients with severe cardiogenic shock with short-term VAD. Thus, we aimed to investigate the efficacy and benefit of levosimendan among patients with short-term VAD.

MATERIALS AND METHODS

Study population

This retrospective study enrolled 29 patients [Figure 1] with cardiogenic shock and end-organ malfunction from January 2017 to May 2019 in our institution. The study protocol was approved by our Institution's Ethics Committee (TSGHIRB number A202005092). All 29 patients developed unstable hemodynamic status despite maximal-dose inotropes and subsequent organ dysfunction. All underwent Bi-VAD implantation based on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 1. Table 1 defined our indications of VAD intervention for these critical patients already with extracorporeal life support (ECLS). Nine of these 29 patients received levosimendan administration immediately after VAD implantation (20-min intravenous bolus infusion at 6–12 μg/kg, followed by a continuous 24-h infusion of 0.1 μg/kg/min), and the other 20 patients without levosimendan were categorized into the control group. The common side effects, such as vasodilation-related hypotension and ventricular arrhythmia, were closely monitored and

Table 1: Indications of ventricular assisted device intervention after extracorporeal life support

ECLS-related
Low ECLS flow
ECLS-related complications
Echocardiography
No outflow from LV
No opening of aortic valve or mitral valve
LV distension with frequent or sustained VT
Systemic malperfusion
Too large dosage of inotropes
Persistent pulmonary congestion
Organ malperfusion despite maximal ECLS support

ECLS=Extracorporeal life support; LV=Left ventricular; VT=Ventricular tachycardia

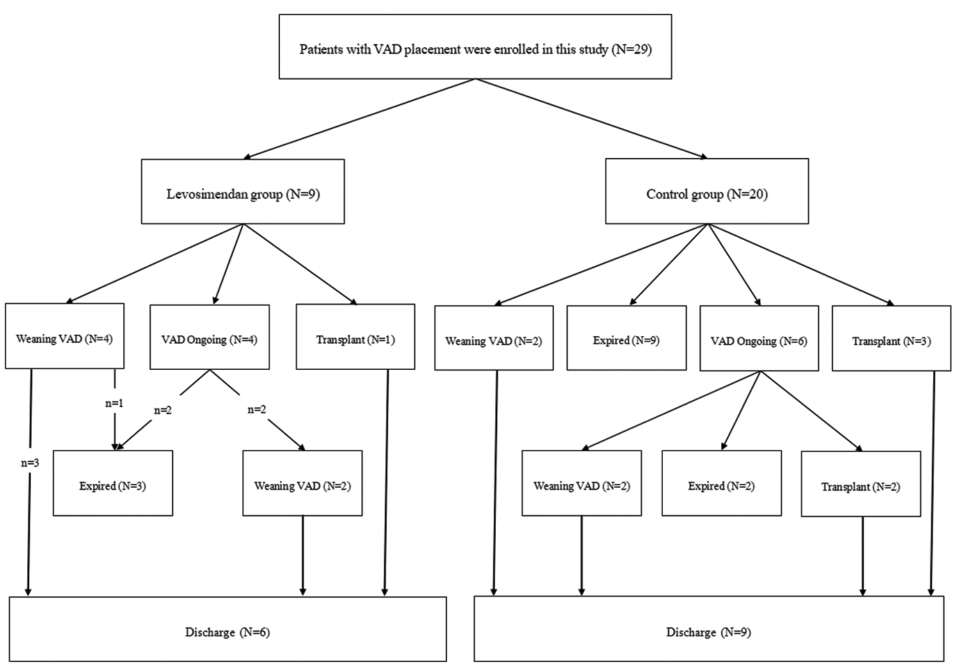

Figure 1: The destiny of patients enrolled in this study. Levosimendan was administered immediately after VAD implantation. Follow-up was completed at 1st, 6th and 12th months. VAD: Ventricular assisted device

recorded. We discontinued levosimendan if frequent ventricular premature beat or if profound hypotension exacerbated, which did not respond to vasopressors. Eventually, all nine 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. Our second inotrope would be 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, [14] and norepinephrine was used in patients with decreased peripheral systemic resistance. [15] As long as the mean arterial pressure (MAP) could be maintained within 70–100 mmHg, the inotropes would be tapered to the minimum as possible. The hemodynamic variation of the two groups was recorded. Diuretic agents, such as eplerenone and furosemide, were prescribed in all cases to maintain a urine output of >0.5 mL/kg/h. Meanwhile, we recorded and compared the biochemistry data, Troponin I and B-Type natriuretic peptide (BNP) levels on day 1 and day 3 after the VAD implant.

Short-term follow-up and assessment of heart function after weaning ventricular assisted device

To evaluate the efficacy of levosimendan, we focus on these patients who had successful weaning. Again, hemodynamic variation and end-organ perfusion were analyzed and compared on day 1 and day 3 after VAD implantation. We also compared the ventilation day and intensive care unit (ICU) stay after weaning VAD. Transthoracic echocardiography was applied to assess the left ventricular ejection fraction (LVEF), pulmonary artery pressure (PAP), left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD) 2 months after VAD weaning. Furthermore, we analyzed the 1-month and 6-month survival rates.

Statistical analyses

SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all analyses. Continuous variables were reported as means ± standard deviations and were compared using the unpaired *t*-test. Kaplan–Meier curve significance was presented using the Gehan–Breslow–Wilcoxon test. $P < 0.05$ was considered statistically significant.

RESULTS

Table 2 presents the patients' characteristics. Characteristics included risk factors of sex, body mass index, body surface area; history of Type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, valve disease, and atrial fibrillation. The etiologies of acute heart failure include dilated cardiomyopathy, ischemic cardiomyopathy, postcardiotomy syndrome, and myocarditis. All patients had abnormal renal function and elevated liver enzyme levels with lactate acidosis initially. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) was maintained within 200–350 mmHg as possible. Echocardiography had impaired systolic function with LVEF of 20.2% ± 7.36% in the levosimendan group and 19.2% ± 10.3% in the control group. Most patients, if not contraindicated, had optimal medical medications, including beta-blocker, diuretics, sacubitril/valsartan, and ivabradine. Nine patients had undergone ECLS cardiopulmonary resuscitation, and four patients had undergone intra-aortic balloon pumping. The mean ECLS-to-VAD interval was 22.1 ± 30.5 h in the levosimendan group (n = 3) and 39.7 ± 99.7 h in the control group (n = 6) (P = 0.612).

Inotrope adjustment, hemodynamic status, and systemic perfusion monitoring

In Table 3, the MAP was significantly lower in the levosimendan group (P = 0.037). The inotropes could be tapered down in both groups. No malignant ventricular rhythm was recorded in all patients within 72 h after levosimendan administration. The levosimendan group had a significant decrease in lactate levels (P = 0.023). Meanwhile, the levosimendan group had significant improvement in PaO_2/FiO_2 ratio (P = 0.048). There was no significant improved variation in serum creatinine, liver enzyme, and total bilirubin levels. There was no significant difference in either BNP or troponin-I variation. As for the conscious improvement, both groups had improvement, although there was no significant difference in improved variation.

Short-term follow-up and assessment of heart function after weaning ventricular assisted device

Table 4 shows the difference between the two groups in patients with successful VAD weaning. The levosimendan group had a significant lower mean MAP (P = 0.004). There was no significant improved variation in liver enzyme level, renal function, cardiac marker levels, lactate level, and consciousness level. The levosimendan group had nonsignificant shorter ventilation day and longer ICU stay. In the 2-month echocardiography follow-up, the levosimendan group had significantly improved LVEF (P = 0.043 and PAP (P = 0.046). However, there was no significant difference in improved variation of LVESD or LVEDD.

Table 2: Characteristics of the patients enrolled

	Mean±SD or *n* (%)		*P*
	Levosimendan group (*n*=9)	Control group (*n*=20)	
Pre-VAD demographics			
Age (years)	57.9±9.7	51.4±13.7	0.086
Female	0	4 (20)	0.042
BMI (kg/m^2)	24.9±3.92	25.3±4.45	0.708
BSA (L/min/m^2)	1.67±0.11	1.87±0.26	0.005
Underlying disease			
Diabetes	3 (33)	5 (25)	0.656
Hypertension	4 (44)	4 (20)	0.244
Hyperlipidemia	3 (33)	5 (25)	0.083
CAD	4 (44)	9 (45)	0.096
Valve disease	4 (44)	9 (45)	0.096
Atrial fibrillation	2 (22)	2 (10)	0.122
Cause			
DCM	2 (22)	3 (15)	0.072
ICM	1 (11)	6 (30)	0.189
Postcardiotomy syndrome	6 (66)	7 (35)	0.317
Myocarditis	0	4 (20)	0.200
CPR	3 (33)	6 (30)	0.864
IABP	1 (11)	3 (33)	0.788
ECLS	3 (33)	6 (30)	0.864
ECLS-to-VAD interval (h)	22.1±30.5	39.7±99.7	0.612
LVEF (%)	20.2±7.36	19.2±10.3	0.787
Hemodynamic and laboratory data			
Total inotropes (mcg/kg/min)	14.54±8.09	14.14±9.05	0.911
MAP (mmHg)	82.0±13.3	74.65±20.4	0.333
Heart rate (beat/min)	91.3±10.9	102.7±24.1	0.092
GCS$^{\#}$ (motor + eye)	7.89±3.22	6.61±3.71	0.278
BNP (10^3 pg/mL)	4141.6±1384.4	2891.6±1583.6	0.007
Troponin-I (ng/ml)	6.74±9.49	5.49±8.51	0.731
AST (U/L)	168.8±259.7	153.75±149.2	0.855
ALT (U/L)	87.11±120.7	94.57±110.4	0.880
Total bilirubin (mg/dL)	2.60±0.75	3.01±4.87	0.427
BUN (mg/dL)	62.3±21.5	44.7±18.9	0.038
Creatinine (mg/dL)	3.18±1.41	2.40±1.31	0.169
PH	7.43±0.04	7.37±0.13	0.227
PaO_2/FiO_2	269.5±73.6	299.0±111.2	0.481
HCO_3^- (mmol/L)	22.5±4.61	19.3±6.49	0.206
Lactate (mmol/L)	4.39±1.64	4.46±3.19	0.954
VAD-associated demographics			
Minimal LVCO (L/min)	4.11±0.49	4.16±1.04	0.902

Contd...

Table 2: Contd...

	Mean±SD or *n* (%)		*P*
	Levosimendan group (*n*=9)	Control group (*n*=20)	
Minimal LVCI (L/min/m^2)	2.48±0.55	2.23±0.56	0.287
VAD duration (days)	35.7±27.7	41.3±14.6	0.710

[#]All patients had endotracheal intubation with ventilator support. Thus the verbal response was unable to assess and not included. BMI=Body mass index; BSA=Body surface area; CAD=Coronary artery disease; DCM=Dilated cardiomyopathy; ICM=Ischemic cardiomyopathy; CPR=Cardiopulmonary resuscitation; IABP=Intra-aortic balloon pump; ECLS=Extracorporeal life support; VAD=Ventricular assist device; LVEF=Left ventricular ejection fraction; LVCO=L-VAD cardiac output; LVCI=L-VAD cardiac index; PaO_2/FiO_2=Ratio of arterial oxygen partial pressure to fractional inspired oxygen; MAP=Mean arterial pressure; GCS=Glasgow Coma Scale; BNP=Brain natriuretic peptide; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; BUN=Blood urea nitrogen; HCO_3^-=Bicarbonate; SD=Standard deviation

Survival rate and weaning rate

Overall, among the nine patients in the levosimendan group, four had successful VAD weaning within 1 month, and another two did within 6 months. However, one of six died of sepsis. One patient underwent heart transplantation within 1 month. The VAD weaning rate was 66.7%, and the 1-year survival rate was 66.7%. Among the 20 patients in control group, two had successful VAD weaning within 1 month and another two did within 6 months. Three patients underwent heart transplantation within 1 month, and another two did within 6 months. The VAD weaning rate was 20%, and the 1-year survival rate was 45%. In summary, the levosimendan group had significant higher weaning rate (66.7% vs. 20%, $P = 0.013$) and higher 1-year survival rate (66.7% vs. 45%, $P = 0.571$), including bridge to recovery and transplantation [Figure 2].

DISCUSSION

Levosimendan, systemic perfusion, and organ preservation

Levosimendan is known to act as both inotrope and vessel dilator, which is also referred to as an inodilator. [16] It acts as a calcium sensitizer by increasing the affinity of myocardial troponin C to calcium. Being different to other inotropes, levosimendan does not increase calcium overload or myocardial oxygen demand.[17] Meanwhile, it also acts as vasodilator by opening the K-ATP channels in both arterial and venous smooth muscle cells, which would reduce the afterload of the left ventricle and preload of the right ventricular, respectively. [18] Moreover, it was reported to open mitochondrial K-ATP channels in the cardiomyocytes, which may provide protection against ischemia–reperfusion injury, oxidative stress, and apoptosis. [19] Patients with cardiogenic shock always need high-dose inotropes for hemodynamic support, which, however, always cause extreme vasoconstriction and lead to subsequent malperfusion of visceral organs. Once VAD is implanted, inotropes should be tapered as soon as possible to alleviate the side effect of vasoconstriction. In our study, the inotropes could be tapered down after the VAD support in both groups. Although there was no difference in inotropes dosage, we observed that levosimendan has lower lactate levels at post-VAD days 1 and 3. In the past decade, most studies on levosimendan emphasized lactate reduction in septic shock, rather than in cardiogenic shock. A meta-analysis conducted by Chang *et al*. reported that levosimendan could significantly reduce serum lactate levels by a mean level of 0.89 mmol/L in patients with septic shock. [20] In our study, the levosimendan group had a more lactate reduction than the control group ($P = 0.023$). We may infer that levosimendan has adjuvant effect for organ perfusion when combined with VAD support. This benefit ought to be attributed to vasodilation by levosimendan, which reversed vasoconstriction by inotropes. As a result, levosimendan would promote better microcirculation perfusion, which was compromised by the high-dose inotropes during the resuscitation. We believe that combined VAD support and levosimendan medication would optimize the end organ perfusion and preservation for these critically ill patients. In the LIDO study, Follath *et al.* reported that levosimendan could reduce the serum creatinine level by > 0.5 mg/dL in more than 50% of patients, whereas only 10% of patients without levosimendan treatment showed a reduction in serum creatinine level in severe low-output heart failure. [11] In our study, the levosimendan group had a consistent reduced mean creatinine level by 0.53 mg/dL, while on the contrary, the control group had an elevated mean creatinine level by 0.33 mg/dL without significance. The Pilot study has reported that levosimendan does benefit the hepatic blood flow in acute decompensated heart failure. [21] Moreover, Brunner *et al*. also reported that levosimendan enables to reduce of apoptosis in human hepatocytes after ischemia–reperfusion injury. [22] In our series, the levosimendan group had a reduction of liver enzyme levels without significance between post-VAD days 1 and 3 [Table 3]. We believe this is because the VAD provided most of the systemic perfusion, and the effect of levosimendan was masked. However, if we take a closer look into the period between baseline and post-VAD day 1, the levosimendan group had reduced liver enzymes, while on the contrary, the control group had elevated liver enzymes without

Table 3: Hemodynamics and end-organ perfusion at postventricular assist device day 1 and day 3 in overall patients enrolled

	Post-VAD day 1		Post-VAD day 3		Variation P*
	Levosimendan group (n=9)	Control group (n=20)	Levosimendan group (n=9)	Control group (n=20)	
Hemodynamic and brain					
Total inotropes (mcg/kg/min)	12.6±6.06	10.1±6.67	5.76±2.80	6.10±4.64	0.162
MAP (mmHg)	82.0±13.3	83.4±19.1	77.6±8.45	90.6±22.8	0.037
Heart rate (beat/min)	91.3±10.9	92.2±18.5	102.4±11.2	87.9±11.6	0.098
Brain					
GCS[#] (motor + eye)	7.11±3.18	6.89±3.39	8.67±1.80	8.17±2.85	0.835
Heart					
BNP (10^3 pg/mL)	3780.3±1611.1	2325.3±1315.4	3040.3±1361.5	2189.2±1672.9	0.378
Troponin-I (ng/ml)	5.21±7.55	6.46±9.28	3.81±7.43	5.34±8.24	0.889
Liver					
AST (U/L)	114.4±234.1	219.2±258.5	42.11±34.0	148.3±174.1	0.124
ALT (U/L)	68.0±134.9	107.2±113.8	31.89±31.6	108.2±109.4	0.937
Total bilirubin (mg/dL)	1.98±1.01	3.84±2.73	1.11±0.75	2.73±1.11	0.223
Kidney					
BUN (mg/dL)	64.6±35.1	39.1±17.7	61.4±30.4	46.4±18.7	0.829
Creatinine (mg/dL)	2.66±1.13	2.27±1.20	2.49±1.39	2.34±1.38	0.366
Oxygenation and perfusion					
PH	7.43±0.05	7.45±0.08	7.44±0.04	7.46±0.06	0.934
PF ratio	298.12±96.6	294.78±65.8	329.67±129.2	265.56±67.7	0.048
HCO_3^- (mmol/L)	21.9±5.25	21.4±4.74	21.6±4.32	23.3±4.71	0.235
Lactate (mmol/L)	3.31±0.89	3.83±3.38	1.29±0.38	2.99±3.80	0.023

[#]All patients had endotracheal intubation with ventilator support. Thus the verbal response was unable to assess and not included; *Variation of hemodynamic was compared between post-VAD day 1 and day 3. VAD=Ventricular assist device; MAP=Mean arterial pressure; GCS=Glasgow Coma Scale; BNP=Brain natriuretic peptide; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; HCO_3^-=Bicarbonate; BUN=Blood urea nitrogen

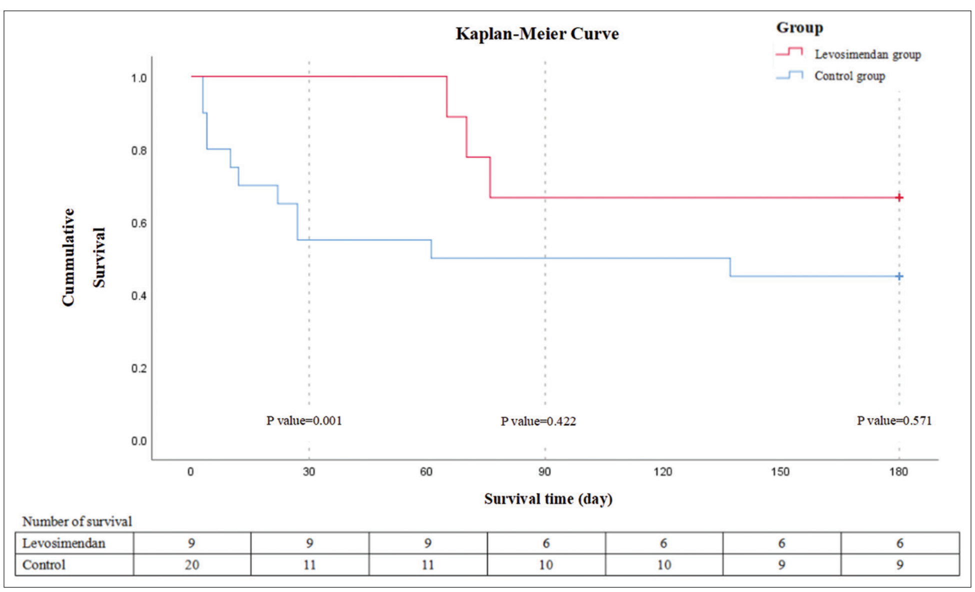

Figure 2: The 180-day Kaplan-Meier survival curve between levosimendan and control group was recoded and compared. The P values at 1, 3 and 6 month are 0.014, 0.422, and 0.571 respectively

Table 4: Variation of hemodynamics and end-organ perfusion in patients with successful ventricular assist device weaning

	Post-VAD day 1		Post-VAD day 3		Variation P*
	Levosimendan group (n=5)	Control group (n=4)	Levosimendan group (n=5)	Control group (n=4)	
Hemodynamic and brain					
Total inotropes (mcg/kg/min)	11.3±7.01	9.81±9.87	5.24±3.63	3.13±4.34	0.868
MAP (mmHg)	80.6±15.4	78.0±16.9	77.6±9.70	99.3±22.1	0.004
Heart rate (beat/min)	69.8±19.3	86.5±25.5	67.0±11.8	91.8±12.6	0.494
Brain					
GCS[#] (motor + eye)	5.20±3.03	7.25±3.78	8.00±2.12	8.25±2.87	0.146
Heart					
BNP (10^3 pg/mL)	3896.8±1515.2	2569.5±1330.2	3034.4±1132.5	2281.8±1869.9	0.393
Troponin-I (ng/ml)	2.75±2.88	11.6±12.6	2.19±2.27	8.82±10.3	0.541
Liver					
AST (U/L)	53.2±35.7	54.8±29.6	33.0±8.19	38.8±7.04	0.849
ALT (U/L)	45.0±15.3	44.3±25.0	34.0±11.8	29.0±8.83	0.642
Total bilirubin (mg/dL)	1.60±0.55	2.53±0.49	0.94±0.36	2.75±0.70	0.066
Kidney					
BUN (mg/dL)	49.8±20.3	49.5±20.8	41.8±13.8	44.0±29.0	0.878
Creatinine (mg/dL)	2.46±1.40	2.13±1.28	2.00±1.01	2.23±1.23	0.158
Oxygenation and perfusion					
PH	7.42±0.06	7.36±0.09	7.45±0.04	7.45±0.07	0.153
PF ratio	313.9±89.3	302.5±31.3	319.5±66.1	265.0±68.0	0.226
HCO_3^- (mmol/L)	21.3±2.09	16.4±5.40	20.5±2.31	21.0±3.92	0.049
Lactate (mmol/L)	3.08±1.00	2.80±1.54	1.10±0.33	1.20±0.63	0.609
ICU course	Levosimendan group (n=5)		Control group (n=4)		Variation P
Short-term result					
Post-VAD ventilation day	25.4±10.9		27.5±9.88		0.774
Post-VAD ICU day	37.2±24.8		32.0±12.5		0.716
2 months follow-up	Baseline		2 months follow up		Variation P*
	Levosimendan group (n=5)	Control group (n=4)	Levosimendan group (n=5)	Control group (n=4)	
Echocardiography					
LVEF (%)	20.4±7.64	17.5±9.57	54.8±21.8	27.0±8.12	0.043
PAP (mmHg)	36.2±6.98	30.0±7.26	29.0±7.78	44.5±25.9	0.046
LVESD (mm)	50.4±16.7	46.5±5.75	42.4±9.43	42.5±9.43	0.255
LVESD (mm)	59.2±14.4	56.5±3.42	53.4±11.1	56.0±4.55	0.299

*P<0.05; Variation were compared between post-VAD day 1 and post-VAD day 3. Echocardiography variation were compared between pre-VAD placement and 2-month follow-up; [#]All patients had endotracheal intubation with ventilator support. Thus, the verbal response was unable to assess and not included. VAD=Ventricular assist device; MAP=Mean arterial pressure; GCS=Glasgow Coma Scale; BNP=Brain natriuretic peptide; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; HCO_3^-=Bicarbonate; BUN=Blood urea nitrogen; ICU=Intensive care unit; LVEF=Left ventricular ejection fraction; PAP=Pulmonary artery pressure; LVESD=Left ventricular end-systolic diameter

significance. We infer that levosimendan effectively increased the hepatic blood flow during this period when the inotropes had not yet been tapered down and the vasoconstriction effect was still present. As for consciousness assessment, both groups had improvement in the Glasgow Coma Scale score, although there was no difference in improved variation. Hansen *et al*. reported that levosimendan is potential to treat pulmonary hypertension in right heart failure[17] due to its vasodilatory effects on the pulmonary vasculature. In our experience, acute pulmonary edema usually resolved 1–3 days after VAD implanted. In this stage, levosimendan might be also helpful in releasing pulmonary vascular tone. We did not routinely record the pulmonary vascular resistance or pulmonary arterial pressure to prove this beneficial effect. However, during VAD support, we observed a significantly better P/F ratio in the levosimendan group [$P = 0.048$, Table 3]. Besides, for those patients with successful VAD weaning, we also noted significantly improved PAP if levosimendan applied [$P = 0.046$, Table 4]. The SURVIVE study[23] and REVIVE II study[24] reported levosimendan had more efficacy in decreasing BNP than dobutamine, which might indicate that levosimendan could increase cardiac contractility and decrease atrial distension. In our series, both groups had BNP decrease immediately after VAD implanted, and the effect persisted all the way down, no matter levosimendan applied or not. In summary, our study demonstrated that levosimendan provided adjuvant effect to perfect the multiple-organ perfusion despite VAD had provided the majority of systemic perfusion for severe patients with cardiogenic shock.

Levosimendan, ventricular assisted device weaning, and follow-up after weaning

In recent decades, temporary VAD was reported as an effective emergent support in patients with cardiogenic shock.[25] It could be used as bridge therapy to recovery, to decision, to heart transplantation, and to intracorporeal VAD if transplantation is limited. [26,27] There is no doubt that either cardiac transplantation or durable intracorporeal VAD should be adopted if weaning temporary VAD fails. In our policy, we would try weaning VAD as first as possible for two reasons. First, not only in Taiwan but also worldwide, cardiac donors are always limited and in shortage. The mean waiting duration for recipient to get a donor's heart is more than 18 months in Taiwan. Second, the durable VAD is only reimbursed and covered for some limited patients by Taiwan National Health Insurance. In literature, the weaning rate is relatively low, and weaning is limited only for some reversible cardiac diseases, such as virus-related myocarditis.[27] Levosimendan has been reported in weaning *extracorporeal membrane oxygenation*; [28-30] however, it was never reported in weaning VAD. Interestingly, in our results, we observed the levosimendan group had a higher weaning rate than the control group [66.7% vs. 20%, $P = 0.013$, Figure 1]. That might infer that levosimendan played as an adjuvant pharmacologic cardiac support once the VAD had stabilized the systemic perfusion and the native cardiac function recovered as well at the same time. Our weaning criteria include LVEF >30%, pump flow of <1.0 L/min, total inotropes dosage <5 μg/kg/min, good end-organ perfusion, absence of pulmonary congestion, and stable hemodynamic status. We did daily bedside echocardiography to assess the heart function, and weaning would be done if the above-mentioned conditions were met. The temporary VAD would be removed as soon as possible to avoid possible complications, such as bleeding, infection, respiratory failure, hemolysis, and neurological dysfunction.[4,5,31] In our patients with successful VAD weaning [Table 4], those with levosimendan applied only had significantly lower MAP. There was no difference in cerebral, hepatic, renal or pulmonary function no matter levosimendan applied or not. In post-VAD care, those patients with levosimendan applied had nonsignificant shorter ventilation day and longer ICU stay. In the 2-month echocardiography, those with levosimendan applied had significantly improved LVEF and lower PAP ($P = 0.043$ and 0.046, respectively). Moreover, they seemed to have less left ventricular remodeling though the difference between LVESD and LVEDD is nonsignificant.

Survival with combined temporary ventricular-assisted device and levosimendan in cardiogenic shock patients

Literature reported a 30-day survival rate of 49%–69% and 1-year survival rate of 37.7%–49% in cardiogenic shock with temporary VAD support, [31-33] which is consistent with our control group. Although levosimendan was reported to reduce mortality in patients with cardiogenic shock, [34,35] no literature can ever prove the efficacy in these extremely critical VAD groups. Obviously, our levosimendan group had significant lower 30-day mortality rate ($P = 0.001$) and nonsignificant 6-month and 1-year mortality rate ($P = 0.422$ and 0.571, respectively) [Figure 2]. Although this is a retrospective study enrolling only nine cases in the levosimendan group, it indeed revealed the potential benefit for these critical patients already with VAD support. Further randomized control trial is necessary for more strong evidence of its efficacy and safety.

Limitations

First, this is a retrospective analysis utilizing chart review. There must be some selection bias during the data collection. Further randomized control trials should be designed for much stronger evidence. Second, the case number enrolled is too small, especially with only nine patients in the levosimendan group. Although we have seen the benefits of levosimendan, there was no significant difference in most of the biochemistry data. We believe the difference would be significant as the cases increase in the future. Third, what we can do to assess the microcirculation perfusion is only the lactate variation. More objective studies, such as whole-body positron emission tomography or organ-specific magnetic resonance imaging scan, are necessary to quantify the tissue perfusion and shock severity. However, it is very difficult to carry out these studies on such critical patients. Finally, more long-term follow-up should be designed, especially on the assessment of the quality of life.

CONCLUSION

Temporary VAD definitely provides the majority of systemic perfusion in patients with cardiogenic shock. Levosimendan, acting as both inotropes and vasodilators, could not only increase the cardiac contractility without increasing intracellular calcium loading but also perfect the microcirculation with the combined use of VAD. Our study demonstrated levosimendan improved VAD weaning rate and mortality rate, and alleviated ventricular remodeling in patients with successful VAD weaning. In short, levosimendan might be considered as an adjuvant therapy for low-INTERMACS patients who have had VAD support.

Data availability statement

The data that support the findings of this study are available from the corresponding author, CS Tsai, upon reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Chien-Sung Tsai and Dr. Chih-Yuan Lin, editorial board members at Journal of Medical Sciences (Taiwan), had no roles in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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