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SHORT COMMUNICATION

Intermittent inotropic therapy with levosimendan vs. milrinone in advanced heart failure patients

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Abstract

Aims Routine, intermittent inotropic therapy (IIT) is still applied in advanced heart failure (HF) patients either as a bridge to definitive treatment or as a mean to improve quality of life (QOL), despite limited evidence to support its' use. Given recent reports of improved QOL and reduced HF hospitalization, with levosimendan compared with placebo in advanced HF patients, we aimed to assess the effects of switching a small group of milrinone-treated patients to levosimendan. This was performed as part of a protocol for changing our ambulatory HF clinic milrinone-based IIT to levosimendan.

Methods and results Single-centre study of consecutive ambulatory advanced HF patients that received ≥4 cycles of once-weekly milrinone IIT at our HF outpatient clinic, who were switched to levosimendan IIT. All patients had left ventricular ejection fraction ≤35%, elevated B-natriuretic peptide (BNP), and were in New York Heart Association Classes III–IV despite maximally tolerated guideline directed medical therapy. Patients were evaluated using BNP levels, echocardiography, cardio-pulmonary exercise test, and HF QOL questionnaire before and after 4 weeks of levosimendan IIT. The cohort included 11 patients, 10 (91%) were male and the mean age was 76 ± 12 years. After 4 weeks of levosimendan therapy, maximal O_2 consumption improved in 8/9 (89%) by a mean of 2.28 mL/kg [95% CI −0.22–3.38, P = 0.05]. BNP levels decreased in 9/11 (82%) levosimendan treated patients, from a median of 1015 ng/L [261–1035] to 719 ng/L [294–739], ($P < 0.01$). QOL as measure by the EQ-5D-5L questionnaire improved in 8/11 (82%) patients after levosimendan IIT, by a median of two points [95% CO −4.14–0.37, P = 0.09]. On echocardiography, peak systolic annular velocity (S') increased after levosimendan IIT by an average of 3 cm/s [95% CI 0.16–2.10, P = 0.03].

Conclusions In this small-scale study of ambulatory advanced HF patients, we observed improvements in right ventricular systolic function, maximal O_2 consumption, and BNP after switching from milrinone to levosimendan based IIT.

Keywords Advanced heart failure; Inotropic therapy; Levosimendan; Milrinone

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Ambulatory inotropic support, either with continuous infusion or intermittent inotropic therapy (IIT) using short term infusions (1–2 times per week) of cyclic adenosine monophosphate (cAMP) dependent agents (e.g. milrinone and dobutamine) is used in ambulatory patients with advanced heart failure (HF). IIT is used for palliation or as bridge to heart transplantation and left ventricular assist device (LVAD) implantation.[1–3] Although there are conflicting data regarding IIT effects on mortality and HF hospitalizations rate in these patients, improvements in functional class and quality of life are more robustly accepted as benefits of IIT.[1]

Levosimendan is a calcium sensitizing agent that induces a limited increase in myocardial oxygen demand, and given the protracted half-life of its metabolite (i.e. OR 1986, half-life 80 ± 36 h), has persistent haemodynamic effects.[4] Levosimendan delivered every other week for 6 h as IIT in a small cohort of patients with advanced HF was recently found to improve QOL and reduce HF hospitalizations.[5] Based on these favourable evidences, patients with advanced HF treated in our ambulatory care clinic, who received at least four consecutive weekly intermittent milrinone infusion cycles, were switched to weekly infusions of levosimendan.

We report here the clinical, laboratory, echocardiographic, and functional capacity data [assessed by cardio-pulmonary exercise test (CPET)] of these patients while on milrinone, as compared with those after four weekly cycles of therapy with levosimendan.

The data that support the findings of this study are available from the corresponding author upon reasonable request. This was a single-centre retrospective cohort study of patients who have been treated with once-weekly 6 h intermittent intravenous milrinone 0.25–0.5 mcg/kg/min for >4 consecutive clinic visits. Patients were switched to intravenous levosimendan at 0.1–0.2 mcg/kg/min for a 6 h period to be repeated every week for 4 weeks. All patients had advanced HF with the following characteristics (in line with recent definitions of advanced HF[6]): left ventricular ejection fraction (LVEF) < 35%, elevated brain natriuretic peptide (BNP) levels, and New York Heart Association (NYHA) Class III–IV despite maximally tolerated guideline-directed medical treatment (GDMT). Seventeen subjects met the above inclusion criteria for the switch. Of these, five were not switched to levosimendan due to: severely reduced blood pressure (*n* = 1), advanced renal disease (*n* = 1), frequent non-cardiac hospitalizations (*n* = 2), and refusal to discontinue milrinone (*n* = 1). One additional patient was not included in this analysis since he did not complete four cycles of levosimendan. This patient received a single dose of levosimendan and subsequently suffered ventricular tachycardia leading to cardiogenic shock and death (*Figure 1*).

All patients completed quality of life (QOL) questionnaires while on milrinone and after completing 4 weeks of levosimendan, laboratory tests including BNP were followed at each clinic visit, routine echocardiography and CPET were performed 1–3 days after completing the last cycle of milrinone and after the 4th cycle of levosimendan. The study was approved by the local Tel-Aviv Medical Center Institutional Review Board (*Figure 2*).

Eleven patients were included in this analysis, their mean age was 76 ± 12 years, and 10 (91%) were male. Mean baseline blood pressure was 111/61 ± 20/12, 91% had an intracardiac defibrillator. All patients received an angiotensin neprilysin inhibitor, beta-blockers, and a loop diuretic, 6 (55%) received mineralocorticoid receptor antagonist, and 2 (18%) received a type 2 sodium-glucose co-transporter inhibitor. During a median follow-up of 83 days [23–140] on milrinone therapy (pre-levosimendan), 3 (30%) of these patients were hospitalized due to HF exacerbation, 2 were hospitalized twice. After 4 cycles of levosimendan therapy, the following changes were observed on CPET: Baseline blood pressure measurements were non-significantly higher on milrinone as compared with on levosimendan (137 ± 74 vs. 128 ± 68, *P* = 0.780 and 0.493 for systolic and diastolic measurements, respectively). Maximal O_2 consumption (VO_2) significantly improved in 8/9 (89%) patients by a mean of 2.28 mL/kg/min [95% CI −0.22–3.38, *P* = 0.05], exercise duration increased in 5/9 patients from a mean of 4.53 ± 1.32 to 5.21 ± 1.35 min (95%CI −0.40–1.35,

Figure 1 Flow chart of patients who met inclusion criteria for the study.

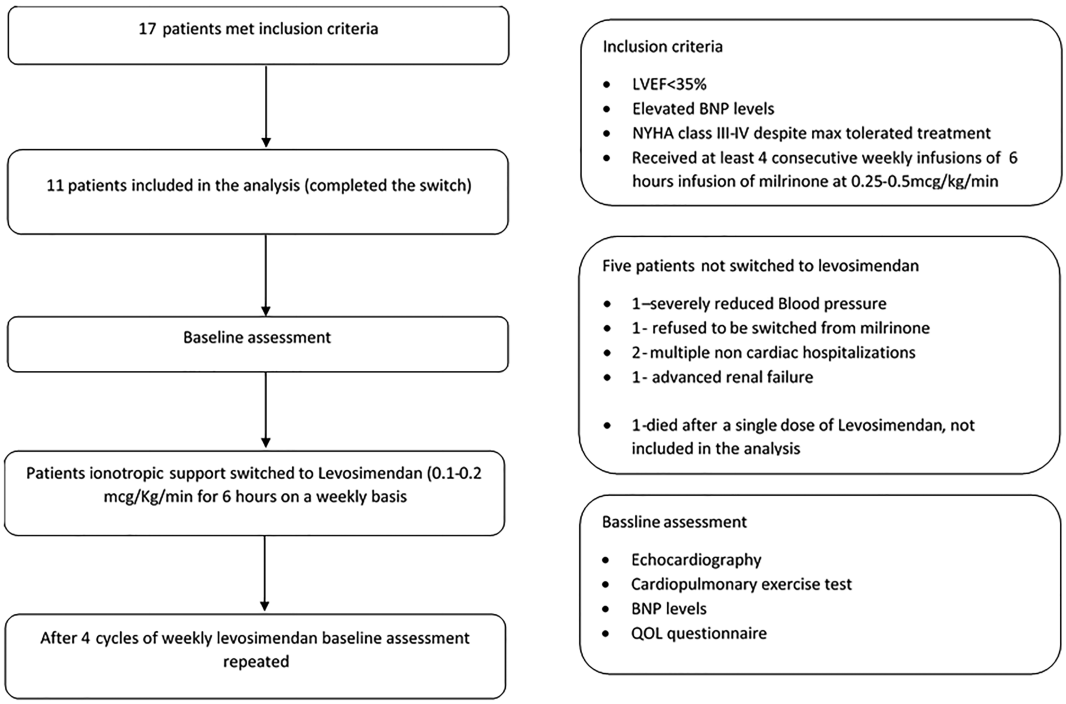
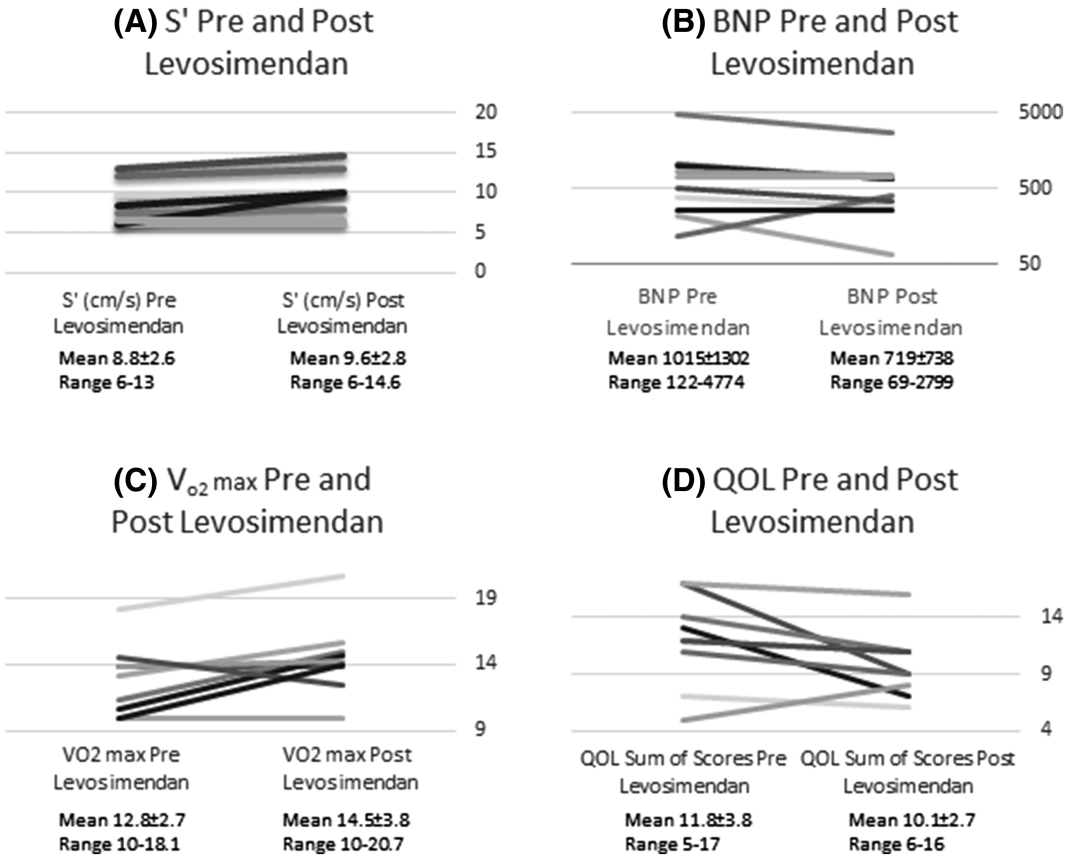


Figure 2 Main characteristics before and after levosimendan treatment. (A) Right ventricular systolic function as measure by S' wave (cm/s) pre-levosimendan (on milrinone) and post 4 cycles of levosimendan treatment. (B) B-type natriuretic peptide levels (pg/mL) pre-levosimendan (on milrinone) and post 4 cycles of levosimendan treatment. (C) Maximal oxygen consumption values (mL/kg/min) pre-levosimendan (on milrinone) and post 4 cycles of levosimendan treatment. (D) Quality of life (QOL) based on sum of scores of five questions in the EQ-5D-5L questionnaire concerning the degree of limitation in different domains of daily living, higher scores meaning greater limitation.



P = 0.382) and the ratio of minute ventilation to the volume of exhaled Co_2 (V_E/Vco_2) decreased in 7/9 patients from a mean of 41.7 ± 9.2 to 37.0 ± 5.1 (95%CI −10.66–1.26, P = 0.107). There were no significant differences in O_2 pulse or maximal heart rate achieved, (*Table* 1). On echocardiography, LVEF, systolic pulmonary artery pressure (SPAP), and tricuspid annular systolic excursion (TAPSE) did not change significantly, whereas the tissue Doppler of the tricuspid lateral annulus (S') improved by an average of 3 cm/s [95% CI 0.16–2.10, P = 0.03]. Average early mitral inflow to mitral annulus velocity ratio (E/e') improved from 14 ± 5 to 10 ± 8 (P = 0.054) on Levosimendan treatment. BNP levels decreased in 9/11 (82%) from a median of 1015 ng/L [261–1035] to 719 ng/L [294–739], ($P < 0.01$). Sum scores of EQ-5D-5L QOL questionnaire (i.e. sum of scores of five questions in the EQ-5D-5L questionnaire concerning degree of limitation in different domains of daily living, higher scores meaning greater limitation) improved in 8/11 (82%) by a median of two points [95% CI −4.17–0.37, P = 0.09].

cAMP-based agents represent the core of inotropic therapy in advanced HF and are delivered either through continuous pumps or as IIT. These drugs are used as IIT for ambulatory HF patients despite substantial limitations, most notably the lack of clear clinical benefit in terms of mortality or HF hospitalization, the association with increased arrhythmic risk and their short half-life (e.g. dobutamine: 2 min).[1–3] These limitations can be partially mitigated by levosimendan given its unique mechanism of inotropic activation (without increasing myocardial oxygen consumption or intracellular calcium levels) and its prolonged haemodynamic effects.[4] The Levosimendan Intermittent administration in Outpatients: effects on Natriuretic peptides in advanced chronic HEART failure (LION-HEART) study randomized 69 patients in 2:1 fashion to 6 cycles 6 h pulse administration of levosimendan vs placebo. NT-proBNP levels significantly improved in the levosimendan arm; furthermore, hospital admissions were reduced (hazard ratio 0.25; 95% CI 0.11–0.56; P = 0.001).[5]

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Table 1 Patients main characteristics before and after 4 weeks of levosimendan treatment

Patient #		Mean ± SD	1	2	3	4	5	6	7	8	9	10	11
VO_2 max (mL/kg)	Mil	12.8 ± 3	13.8	13.1	11.3	10.6	18.1	13.9		14.6	10		10
	Levo	14.5 ± 3	13.9	15.6	15	14.7	20.7	14.2		12.4	10		14
Exercise duration, min	Mil	4.53 ± 1.3	4.35	6.11	2.31	3.08	7.34	5.35		4.02	5		5.27
	Levo	5.21 ± 1.4	4.01	6.26	5.51	4.27	7.19	6.29		3.06	3.29		6.58
Ve/VCO_2	Mil	42 ± 9	44	34	37	42	29	38		48	60		43
	Levo	37 ± 5	43	33	35	39	29	32		42	36		44
Maximal heart rate, bpm	Mil	105 ± 39	98	87	101	101	148	94		52	77		184
	Levo	104 ± 33	107	106	97	98	150	114		50	68		150
O_2 pulse, mL/beat	Mil	13 ± 6	15	19	8	7	9	13		23	7		12
	Levo	12 ± 3	8	14	10	10	10	11		19	12		12
LVEF, %	Mil	32 ± 6	30	25	35	20	30	35	35	35	35	30	30
	Levo	31 ± 8	25	30	35	20	35	40	25	45	35	25	30
E/e′	Mil	14 ± 5	9	11	11	28	18	21	14	11	16		13
	Levo	10 ± 8	3	5	5		5	25	13	13	16		9
SPAP	Mil	44 ± 17	27	27	70	46	42	49	30	39	43	70	20
	Levo	43 ± 17	26		65	27	35	55	41	34	43	73	27
S′ wave	Mil	9 ± 3		6	7.5	6	9.7		12	13	6.5	9.9	8.4
	Levo	10 ± 3	6	6	8	10	10	10	13	14.6	6.5	11	9.9
QOL	Mil	60 ± 24	5	70	60	60	80	90	75	50	40	65	
	Levo	67 ± 23	50	80	27	98	100	80	70	50	55	60	65
Sum of scores	Mil	12 ± 4	17	12	14	13	7	5	11	12	17	11	
	Levo	10 ± 3	9	11	11	7	6	8	9	11	16	12	11
BNP, pg/mL[a]	Mil	723 [261–1035]	1035	221	4774	1025	377	851	122	511	723	1275	265
	Levo	664 [294–739]	687	69	2799	664	294	739	398	339	723	949	254

BNP, B-type natriuretic peptide; EF, ejection fraction; E/e′, average early mitral inflow to mitral annulus velocity ratio; Levo, levosimendan; Mil, milrinone; QOL, quality of life (0–100); SPAP, systolic pulmonary artery systolic pressure (mm/Hg) assessed by echocardiography; SVI, stroke volume index as assessed on echocardiography by multiplying the velocity time integral through the aortic valve by the aortic valve area, divided by body surface area. Sum of scores—summation of all scores to define degree of limitation in five domains of QOL, with higher scores signifying greater disability.
[a]Data for BNP is presented as median [interquartile range].

Advanced HF patients at our facility were routinely treated with milrinone IIT, and we observed a reduction in BNP levels and an improvement in functional capacity in these patients (unpublished data). However, due to the results of the LION-HEART study, we chose to examine the potential beneficial effect of levosimendan IIT in previously milrinone-treated patients. In this small observational study, levosimendan as compared with milrinone IIT, was associated with an improvement in maximal oxygen consumption and with a trend towards improvement in most exercise capacity indices on CPET (i.e. exercise duration and ventilatory efficiency). Right ventricular and LV diastolic function as assessed by echocardiography improved, BNP levels were significantly reduced, and a borderline improvement in QOL was recorded. These observations were in line with a non-significant decrease in blood pressure on levosimendan and might be in-line with levosimendan's mechanism of action (i.e. lusitropic effect without increasing oxygen demand accompanied with prolonged afterload reduction). Although no meaningful improvement in LV systolic performance was evident (i.e. O_2 pulse and LVEF), markers of congestion (BNP and E/e′) along with RV function and load (S′ and SPAP) ameliorated, possibly leading to the observed improvement in functional capacity as assessed by CPET. These observations add to the results of recent levosimendan IIT studies and merit further prospective larger scale clinical studies to assess the performance of IIT with levosimendan.

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