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A favorable alliance between repetitive use of levosimendan and advanced heart failure: Polish two-centered inpatient perspective in need of validation

Short title: Repetitive use of levosimendan in AdvHF

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INTRODUCTION

The prevalence of advanced heart failure (AdvHF) is estimated to be 1%–10% of heart failure (HF) patients [1]. Although the evidence-based therapies improved outcomes in chronic HF [2], the outcomes in AdvHF remain poor [3]. 2021 European Society of Cardiology (ESC) allows for inotropic agents in patients with acute decompensation of HF with hypotonia and hypoperfusion who do not respond to conventional treatment (class IIb) [2]. Levosimendan is an inotrope that augments cardiac contractility by increasing calcium sensitivity, it promotes vasodilatation and cardioprotection [3, 4]. Inotropes without an adrenergic mechanism, such as levosimendan, may be preferred in patients on β -blockers [2, 4].

This study aims to present the first Polish experience on the efficacy and clinical outcomes of repetitive use of levosimendan in AdvHF.

METHODS

We conducted a prospective, observational, real-life study in two Polish cardiology centers (Lodz, Gdansk) between 2015 and 2018. The institutional review board approved the study (approval No. RNN/231/19/KE, KE/335/20). The study enrolled 46 inpatients meeting the

criteria of AdvHF [1, 2]: (1) symptoms of HF in New York Heart Association (NYHA) class III or IV; (2) left ventricle ejection fraction (LVEF) $\leq 30\%$; (3) pulmonary or systemic congestion requiring intravenous (IV) diuretics or low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 visit or hospitalization in the last 12 months; (4) severe impairment of exercise capacity of cardiac origin. The exclusion criteria were: (1) age <18 years old; (2) symptomatic hypotonia; (3) estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m²; (4) non-ischaemic liver injury; (5) hypersensitivity to levosimendan; (6) pregnancy or the peripartum period. Patients were receiving appropriate treatments for HF with reduced ejection fraction (HFrEF), including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) or angiotensin receptor/neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRA), and, when indicated, diuretics, cardiac devices and inotropic agents.

All patients received IV infusion of levosimendan with a rate of 0.1 $\mu\text{g}/\text{kg}/\text{min}$. up to 12.5 mg or maximum tolerated dose within 24-48 hours. Patients who received single infusion were defined as non-repetitive, while patients who received >1 infusion were defined as repetitive. Each repetitive infusion was completed during planned hospitalization >2 days and reimbursed by the National Health Found (JGP group: E50, E52 or E53G). The interval between infusions varied from 2 to 4 weeks. The enrolment to the repetitive group was limited to patients who agreed to repetitive infusion within the next 2-4 weeks. A complete history and transthoracic echocardiography was taken before each infusion. A physical examination, lab tests and electrocardiograms were taken before and after each infusion.

Subjects were followed-up via an on-site visit or a phone call every 3 months for 1 year after the first infusion. If subject did not carry out the visit as planned a phone call to his family was made to confirm the death. In total, 95 variables were analyzed.

The endpoint consists of death or heart transplantation (HTx) or ventricular assist device (VAD) therapy within 1 year of follow-up in the two treatment groups.

Statistical analysis

Baseline characteristics of participants were presented as means with SD or medians with interquartile range depending on distribution for continuous variables or as number of subjects and percentages for categorical variables. Distribution of continuous variables was evaluated using Shapiro-Wilk test. To compare differences between groups t-Student, Welch's, Mann-Whitney U test, Wilcoxon signed rank and χ^2 tests (Pearson's, Fischer's, McNemar's with Yates' correction if necessary) were used. To identify the treatment regimen influence on

patients' survival time a survival analysis using Kaplan-Meier curves compared with Mantel-Cox test were employed. To identify whether baseline parameters could predict the study endpoint univariate logistic regression was used. A $P < 0.05$ was deemed significant. All analyses were made using Statistica 13 and GraphPad Prism 8 software.

RESULTS AND DISCUSSION

A baseline characteristics of patients' non-repetitive and repetitive are presented in Supplementary materials, *Table S1*. A total of 30 patients received single infusion, while 16 patients received >1 infusion (10 patients received 2 infusions, 2 patients received 3 infusions, and 4 patients received 4 infusions).

The endpoint occurred in 16 (53%) non-repetitive vs. 6 (38%) repetitive patients (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.15–1.82; $P = 0.42$); within hospitalization in 10 (33%) vs. 4 (25%) patients, respectively.

The survival curve showed that non-repetitive group was characterized by an over 6-fold higher risk of death compared to repetitive group (hazard ratio [HR], 6.63; 95% CI, 1.96–22.41; $P = 0.002$). The median survival time between repetitive and non-repetitive group was 145 (82–185) days vs. 57 (38–64) days, respectively (**Figure 1**).

The results of univariate analysis are showed in Supplementary materials, *Table S2*.

The signs and symptoms of HF, laboratory and electrocardiographic parameters in both groups at baseline and after infusion, and echocardiographic parameters in the repetitive group at baseline and before the last infusion are presented in Supplementary materials, *Tables S3, S4* and *S5*.

In both groups we observed a reduction in NT-proBNP, while in the repetitive group we observed a reduction in left ventricle end-diastolic/end-systolic diameters/volumes without an improvement in LVEF.

The study shows that repetitive use of levosimendan does not reduce the risk of death or HTx or VAD, but it increases the probability of 1-year survival in AdvHF, and reduces the signs and symptoms of HF.

The pharmacotherapy for HFrEF included the drugs of I class recommendations. Unfortunately, the study was conducted before gliflozins were established as fundamental HFrEF pharmacotherapy [2]. It is worth mentioning that only 60% of patients in the non-repetitive group and 69% in the repetitive group used ACEI/ARB/ARNI, what was limited by hypotension in AdvHF. Although the percentage of patients receiving ACEI/ARB/ARNI did not change significantly after infusion, we observed an increase in ARNI use from 12% to 40%

in the repetitive group. The use of MRA was significantly higher in the repetitive group (94% vs. 60%; $P = 0.02$) what resulted from higher eGFR in this group.

In our study, pharmacotherapy with beta-blocker, MRA and diuretic was associated with lower risk of endpoint occurrence.

Levosimendan, compared to other inotropes, reduces the signs and symptoms of HF [3, 5–8], and mortality [5, 7, 8]. However, metaanalyses [9, 10] and SURVIVE study [11] showed that levosimendan does not reduce mortality.

Some trials investigated repetitive use of levosimendan in AdvHF [12–14]. Both studies, LION-HEART and LAICA, showed that intermittent ambulatory use of levosimendan in AdvHF reduces HF hospitalizations [12, 13]. In contrast, the LevoRep study did not show improvements in quality of life or functional capacity after levosimendan use [14]. The doubts about intermittent use of levosimendan in AdvHF might be cleared up shortly by a multicentre, randomized, double-blind, placebo-controlled LEIA-HF study in which 350 patients with AdvHF are planned to be enrolled [15].

Although the data concerning mortality in patients treated with levosimendan is inconsistent, our study shows that repetitive use of levosimendan might be beneficial in AdvHF.

Limitations

The study was conducted on small and disproportionate groups of patients, resulting from a small population of AdvHF patients and high levosimendan costs. The real-life protocol makes the study less robust and reliable compared with double-blinded and randomized trials. There is a missing data in echocardiographic parameters after infusion in non-repetitive group.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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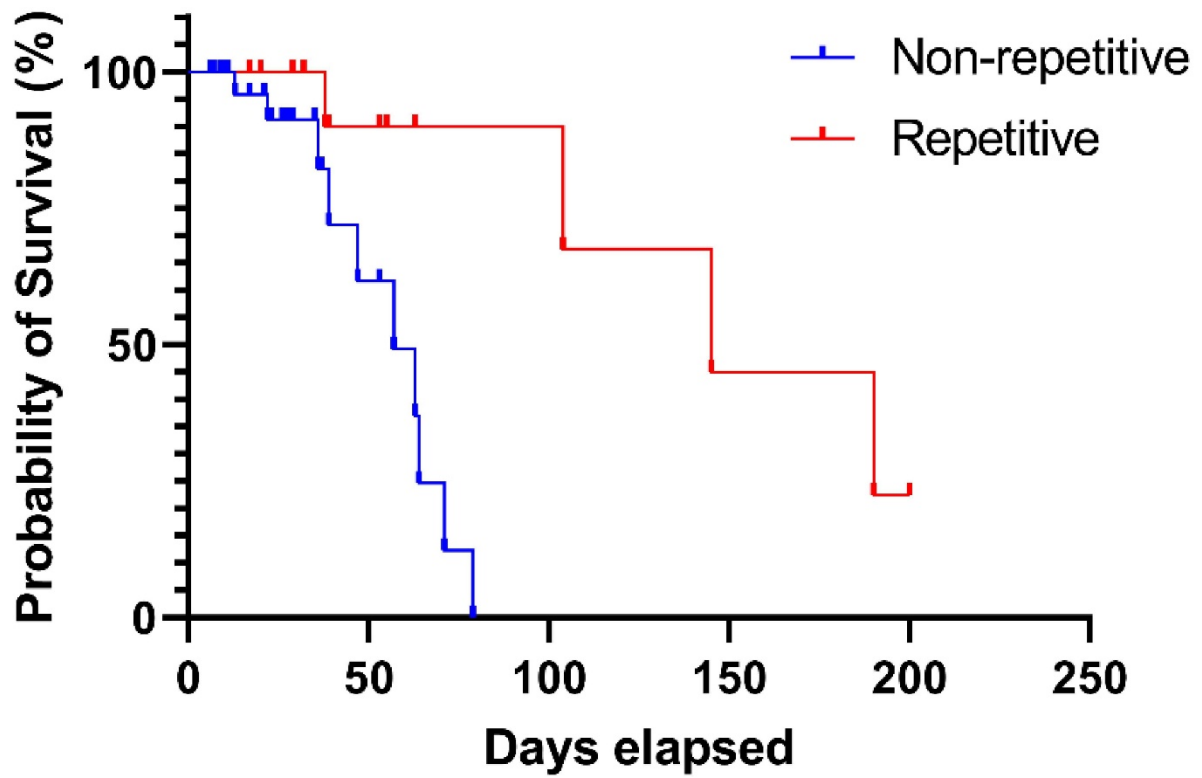
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	Median survival time (days)	Curve comparison (<i>P</i> -value)
Non-repetitive	57 (38-64)	0.002
Repetitive	145 (82-185)	

Data are presented as median (Q1-Q3)

Figure 1. Kaplan-Meier estimates of survival in the two treatment groups