A promising new inotrope: levosimendan

Umut verici yeni bir inotropik ajan: Levosimendan

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ABSTRACT

Intravenous positive inotropic agents are commonly used to treat the patients with acute decompensated heart failure due to left ventricular systolic dysfunction. Although these agents seem to be beneficial for improving symptoms of heart failure in the short-term; it has been reported that they are associated with increased mortality and morbidity. Levosimendan is a new calcium sensitizer and K-ATP channel opener, has emerged as an alternative option of pharmacologic inotropic support in patients with decompensated heart failure. Recent reports on levosimendan's use in severe heart failure demonstrated that this agent is more favorable drug compared with conventional inotropic agents, though its better profile in terms of myocardial efficiency has not been completely understood. This review summarizes the evidence from current scientific literature including our recent trials regarding the mechanism of action, efficiency and the use of levosimendan.
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Key words: Levosimendan, heart failure, positive inotropic agents, clinical trials

ÖZET

Pozitif inotropik ajanlar sol ventrikül sistolik disfonksiyonuna bağlı dekompanse kalp yetersizliği tedavisinde sık olarak kullanılmaktadır. İnotropik ajan olarak kullanılan fosfodiesteraz inhibitörleri ve beta-adrenerjik agonistler, kalp yetersizliği semptomlarını kısa süreliğine etkili olarak düzeltiği halde, bu ilaçların kullanımının mortalite ve morbiditede artış yaptığı bildirilmiştir. Levosimendan yeni bir kalsiyum duyarlaştırıcısı ve K-ATP kanal açıcısı olup, dekompanse kalp yetersizliği hastalarında alternatif bir inotropik ajan olarak ortaya çıkmıştır. Yapılan son çalışmalar, miyokardiyal etkinliği tam anlaşılmamış olmasına rağmen, diğer konvansiyonel inotropik ajanlara kıyasla, ileri kalp yetersizliğinde levosimendan kullanımının daha uygun olduğunu ortaya koymuştur. Bu derleme, çeşitli klinik durumlarda levosimendan kullanımının etkinliği üzerine yapılan bilimsel çalışmaları özetlemektedir. *(Anadolu Kardiyol Derg 2010; 10: 176-82)*
Anahtar kelimeler: Levosimendan, kalp yetersizliği, pozitif inotropik ajanlar, klinik çalışmalar

Introduction

Acute heart failure (HF) is an important health problem because of its high prevalence, high rates of mortality, hospitalization and significant healthcare costs, with the numbers of patients readmission for acute HF increasing due to ageing populations and improvements in the treatments of coronary heart disease and chronic heart failure (1). Patients with acute HF have an estimated one-year mortality of 30-50% (2). Acute heart failure is responsible for 2-3% of all hospital admissions and 45% of the patients will be admitted to hospital at least once (1). Therefore, therapeutic approaches are therefore needed to alleviate symptoms, stabilize the hemodynamics of the patients and improve their quality of life and survival.

Conventional inotropic agents are one of the therapeutic options for treating acute HF due to systolic dysfunction. In recent decades, clinical experience has supported the use of these drugs and adrenergic stimulants such as dobutamine, which have come to be used more than phosphodiesterase (PDE) III inhibitors, such as milrinone. However, the clinical information on the efficacy and safety of these therapeutic groups is limited and sometimes suggests they may have significant adverse effects (3). These findings may be related to the fact that these drugs increase myocardial concentrations of cyclic adenosine monophosphate (cAMP), producing an increase in intracellular calcium that possibly leads to myocardial cell death and/or increases fatal arrhythmias (4). A new pharmacological group of positive inotropes known as calcium sensitizers has recently appeared.

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The main representative of this new group is levosimendan. The clinical development of this agent has gained the interest of clinicians due to the efficacy and safety of this inotropic drug in the treatment of patients with acute HF.

Experimental studies indicated that levosimendan increased myocardial contractility, improved hemodynamics and caused dilatation both the peripheral and coronary vessels (5, 6). Subsequent experiences in small-scale studies and randomized clinical trials have led to greater interest in the use of this drug for the short-term support of impaired cardiac function in various clinical settings.

The aim of this review is to summarize the available clinical studies including our recent trials about the mechanism of action, efficiency and the use of levosimendan in different clinical situations.

Mechanism of effects

Levosimendan belongs to the so-called group of "calcium sensitizers" that includes several other substances that share the ability of increasing sensitivity of myofilaments to calcium, leading to increased myocardial contraction without increasing intracellular cAMP or intracellular calcium concentration. This new agent seems to be associated with fewer adverse effects and lower arrhythmogenic potential compared with traditional inotropes or inodilators.

Levosimendan displays calcium-dependent binding to the N-terminal domain of cardiac troponin C (TnC) with a higher affinity at high calcium concentrations and a lower affinity at low calcium concentrations (7). By stabilizing the calcium-TnC complex, levosimendan inhibits the troponin I (TnI) effect and prolongs the actin-myosin cross-bridge association rate. This positive inotropic effect is obtained without increasing intracellular calcium concentration or with a significant increase in myocardial oxygen demand, usually seen with other inotropes (8, 9).

Levosimendan was also shown to open the mitochondrial ATP-dependent potassium (K) channels in myocytes and vascular smooth muscle cells, which causes vasodilatation (10, 11). These properties decrease both preload and afterload, increase coronary, other organ blood flow (12, 13). Finally, levosimendan also opens the cardiac mitochondrial of ATP-sensitive K+ channels, a potentially cardioprotective mechanism linked to the preconditioning in response to oxidative stress (14, 15).

Although oral levosimendan has high bioavailability (approximately equal to 85%), in clinical practice it has been hitherto administered intravenously. Levosimendan has total clearance of 175-250 mL/h/kg and most importantly a short half-life (about 1.5 hours). Therefore, this drug has a special pharmacokinetic interest: it is one of the few drugs used in cardiovascular medicine, which prolonged action is not due to the drug itself but is mainly due to its active metabolite OR-1896 (approximately 80 hours half life). This metabolite reaches a peak plasma concentration about 2 days after the termination of the infusion and exhibits hemodynamic effects similar to those of levosimendan (16). Because of the long half-life of the active metabolite, these effects last for up to 7 to 9 days after discontinuation of a 24-hour infusion of levosimendan (17). This long half-life is markedly increased in patients with severe chronic renal failure or end-stage renal disease, undergoing hemodialysis as compared with healthy subjects (18). Other metabolites with possible pharmacologic effect are N-conjugated OR-1855 (M7), N-hydroxylated OR-1855 (M8), N-hydroxylated OR-1896 (M10), O-glucuronide OR-1896 (M9) and O-sulfate (M11) of N-hydroxylated OR-1896.

The use of levosimendan in different clinical conditions

Acute heart failure

Several clinic studies confirm the beneficial effect of levosimendan on short-term clinical signs and symptoms, and hemodynamics in patients with acute HF. The Levosimendan Infusion versus DObutamine (LIDO) study (19) enrolled 203 patients with severe low-output acute HF and compared the effects of levosimendan with those of dobutamine in a double-blind fashion over 24 hours. The primary endpoint was the proportion of patients with hemodynamic improvement (defined as an increase of 30% or more in cardiac output and a decrease of 25% or more in pulmonary-capillary wedge pressure (PCWP)) at 24 hours. The primary hemodynamic endpoint was achieved in 29 (28%) levosimendan-group patients and 15 (15%) in the dobutamine group (hazard ratio (HR) 1.9 [95% CI 1.1-3.3]; p=0.022). At 180 days, 27 (26%) levosimendan-group patients had died, compared with 38 (38%) in the dobutamine group (p=0.029).

The CAlcium Sensitizer or Inotrope or NOne in low-output heart failure study (CASINO) is a randomized, double-blind, double-dummy and parallel-group study (20). This study was designed to compare the safety and efficacy of levosimendan, dobutamine and placebo in patients with decompensated heart failure. The primary endpoint was the composite of death or rehospitalization due to heart failure deterioration. Levosimendan showed a significant survival benefit in these patients whereas dobutamine appeared to increase mortality.

The Randomized stUdy on Safety and effectivenesS of Levosimendan in patients with left ventricular failure due to an Acute myocardial iNfarct (RUSSLAN) (21) evaluated the safety and efficacy of levosimendan in patients with left ventricular (LV) failure complicating acute myocardial infarction. This study had a double-blind and placebo-controlled design. The incidence of ischemia and/or hypotension was similar in all treatment groups (p=0.319). A higher frequency of ischemia and/or hypotension was only seen in the highest levosimendan dose group. Levosimendan-treated patients experienced lower risk of death and worsening heart failure than patients receiving placebo, during both the 6-hour infusion (2.0% vs 5.9%; p=0.033) and over 24h (4.0% vs 8.8%; p=0.044).

Mortality was lower with levosimendan compared with placebo at 14 days (11.7% vs 19.6%; hazard ratio 0.56 [95% CI 0.33-0.95];p=0.031) and the reduction was maintained at the 180-day retrospective follow-up (22.6% vs 31.4%; 0.67 [0.45-1.00], p=0.053).

In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial, levosimendan significantly improved a composite of clinical signs and symptoms of acute decompensated HF over 5 days as assessed by patients and their physicians (22).

The REVIVE-2 trial randomized 600 patients-with acute decompensated HF, left ventricular ejection fraction (LVEF) <35% and resting dyspnea despite IV diuretics-to a 12-µg/kg bolus of levosimendan followed by a 24-hour 0.2-µg/kg/min infusion of levosimendan or matching placebo. For patients in both groups, physicians continuously adjusted conventional background thera-

py as needed (23). Worsening HF requiring rescue IV therapy developed in 15% of patients in the levosimendan group and 26% of patients in the control group. Such therapy was prompted primarily by worsening dyspnea, pulmonary edema, or renal function. The overall composite endpoint was significantly improved in the levosimendan group compared to the control group, as a result of more patients indicated improvement and fewer exhibited deterioration or lack of response at each of the time points. However, the beneficial clinical responses with levosimendan were associated with increased incidence of hypotension (49.2 vs. 35.5%), headache (29.4 vs. 14.6%), episodes of ventricular tachycardia (24.1 vs. 16.9%), ventricular extrasystoles (7.4 vs. 0.2%) and atrial fibrillation (8.4 vs. 0.2%), and a higher early mortality rate (15.1 vs. 11.6%), although no significant survival differences were present at the prespecified time points of 31 and 90 days.

The SURVival of patients with acute HF in need of IntraVEnous inotropic support (SURVIVE) study (24) was the first prospective, double-blind, randomized trial utilizing mortality as the primary endpoint in evaluating the efficacy of levosimendan as compared with dobutamine. A total of 1327 patients hospitalized for acute decompensated heart failure, LVEF ≤30%, not responding to intravenous diuretics and vasodilator therapy were included in the study. The primary endpoint of the study was all-cause mortality in 180 days. Secondary endpoints include the number of days alive and out of the hospital during the 180 days of the trial, all-cause mortality during 31 days, cardiovascular mortality during 180 days and global assessment at 24 hours. At 180 days, no differences in mortality have been observed between patients treated with levosimendan and dobutamine [26 vs. 28%, respectively, HR 0.91 (95% CI 0.74-1.13); p=0.401] (25). A secondary endpoint, B-type natriuretic peptide (BNP) level was significantly reduced in the levosimendan arm compared with the dobutamine arm.

In a recent study, Cohen-Solal et al. (26) retrospectively assessed the association between changes in BNP levels and all-cause mortality in patients from the SURVIVE trial. B-type natriuretic peptide_levels were measured at baseline and at days 1, 3, and 5. A patient was classified as a "responder" if the follow-up BNP level was 30% lower than baseline BNP. The relationship between early BNP response and subsequent all-cause mortality over short- (31-day) and long-term (180-day) intervals was evaluated. Of 1.327 SURVIVE patients, this analysis included 1.038 who had BNP samples at both baseline and day 5. Responders at days 1, 3, and 5 had lower all-cause mortality than did nonresponders (p=0.001), with day-5 levels showing superior discriminating value. Short-term all-cause mortality (31-day) risk reduction was 67% in day-5 BNP responders compared with nonresponders, whereas long-term (180-day) all-cause mortality risk reduction was 47%. Therefore, it was concluded that patients with BNP reduction on treatment for acute HF had reduced mortality risks (31- and 180-day) compared to those with little or no BNP decrease.

Mabezaa et al. (27) assessed outcomes of SURVIVE patients who were on β-blocker therapy before receiving a single intravenous infusion of levosimendan or dobutamine (27). Cox proportional hazard regression revealed all-cause mortality benefits of levosimendan treatment over dobutamine when the SURVIVE population was stratified according to baseline presence/absence of chronic HF history and use/non-use of β-blocker treatment at baseline. All-cause mortality was lower in the chronic HF/levosimendan group than in the chronic HF/dobutamine group, showing treatment differences by HR at days 5 (3.4 vs. 5.8%; HR 0.58, 95% CI 0.33-1.01, p=0.05) and 14 (7.0 vs. 10.3%; HR 0.67, 95% CI 0.45-0.99, p=0.045). For patients receiving β-blockers (n=669), mortality was significantly lower for levosimendan than dobutamine at day 5 (1.5 vs. 5.1% deaths; HR 0.29; 95% CI 0.11-0.78, p=0.01).

Although these trials demonstrated that levosimendan is more favorable drug compared with conventional inotropic agents and placebo in advanced HF, the exact mechanism of its better profile in terms of myocardial efficiency has not been completely understood. Starting out of this point, we assessed the effects of levosimendan therapy on left atrial (LA) and LV diastolic functions in patients with advanced HF to clarify the mechanism of the more favorable effects of this agent in two different randomized controlled comparative studies. In one of these studies, we compared the effects of levosimendan and dobutamine on LA functions in patients with decompensated HF (28, 29). The LA has multiple functions acting as a conduit (for blood from the pulmonary veins to the left ventricle) during early diastole, as an active contractile chamber that augments LV filling in late diastole, as a suction source that refills itself in early systole and as a reservoir during ventricular systole (30). Overall, atrial contraction contributes to about 30% of cardiac output (31). Although the effects of levosimendan on LV function have been studied, its effect on LA function is poorly understood despite its key role in optimizing LV function. Seventy-four patients (mean age 64±10 years) with decompensated HF and LVEF ≤35% were randomized to levosimendan (n=37) and dobutamine (n= 37) groups. Ejection fraction was significantly increased in both groups. The levosimendan group had greater decrease in BNP and active emptying fraction at 24 hours compared with dobutamine group. The passive emptying fraction, E/e ratio and the deceleration time of the E wave were significantly improved in levosimendan but not in dobutamine group. Levosimendan-induced percent change of BNP was significantly correlated with the percent change of E/e and passive emptying fraction (r=-0.38, p<0.05 and r=0.48, p<0.005, respectively). In that study, we showed the novel inodilator agent levosimendan improved LA performance in patients with severe HF receiving optimal conventional treatment. Levosimendan-treated patients had a greater decrease of BNP than dobutamine (28, 29).

In the other randomized prospective trial, we also compared the effects of levosimendan and dobutamine on LV diastolic functions using the conventional and tissue Doppler imaging in patients with decompensated advanced HF (32). Sixty-three patients (mean age 65±9 years) refractory to conventional therapy with LVEF ≤35% and diastolic LV dysfunction due to idiopathic or ischemic cardiomyopathy were enrolled and were randomized to levosimendan (n=33) or dobutamine (n=30). In this study, the improvement of LV ejection fraction and volumes were similar in both levosimendan and dobutamine groups. However, levosimendan but not dobutamine group showed a significant increase of A wave (p<0.05), deceleration time (p<0.005) and a significant reduction of E wave (p< 0.0001), E/A (p< 0.0005) and E/e (p<0.001) ratios. The levosimendan group had also a greater decrease in BNP at 24 hours compared with dobutamine group (p<0.005). The percent

change of BNP in levosimendan group was significantly correlated with the percent change of E/e ratio and deceleration time (r=-0.42, p<0.01 and r=0.58, p<0.005, respectively) (32). Our studies results suggest that levosimendan but not dobutamine may improve LA and LV diastolic functions and this may help to explain the more beneficial effects of levosimendan in patients with advanced HF.

A series of dose-ranging and tolerability studies of intravenous levosimendan in patients with HF were also reported. In a double-blind, placebo-controlled, randomized dose-ranging study (33)the effects of different doses of intravenous levosimendan compared with placebo and dobutamine in patients with NYHA class II-IV HF were assessed. Levosimendan was given as a 10 min loading dose of 3, 6, 12, 24 or 36 µg/kg, followed by a 24-h infusion of 0.05, 0.1, 0.2, 0.4 or 0.6 µg/kg/min, respectively. Levosimendan exerted a dose-dependent effect on cardiac output, stroke volume and PCWP. At 23-24 hours, all doses of levosimendan produced significantly larger decreases in PCWP than dobutamine and infusions of 0.4 and 0.6 µg/kg/min produced significantly larger increases in cardiac output. In another double-blind, placebo-controlled, randomized study, advanced HF patients with LV systolic dysfunction were randomized to levosimendan or placebo treatment groups (34). Drug infusions were up-titrated over 4 hours from an initial infusion rate of 0.1 microg x kg (-1) x min (-1) to a maximum rate of 0.4 microg x kg(-1) x min(-1) and maintained at the maximal tolerated infusion rate for an additional 2 hours. Levosimendan was associated with dose-dependent increases in stroke volume and cardiac index and decline in PCWP that were significantly different from placebo at all doses tested. Heart rate did not increase at the two lowest infusion rates of levosimendan but increased with further up-titration to a maximal increase of 6±1 bpm at 6 hours (vs. 1±1 bpm for placebo).

On the basis of these studies, the recent European Society of Cardiology guideline on the diagnosis and treatment of acute HF from the suggested the use of levosimendan in patients with symptomatic low cardiac output HF secondary to cardiac systolic dysfunction without severe hypotension (recommendation level IIb, level of evidence B) (35). However, despite strong evidence from randomized clinical trials, levosimendan has not been approved for use in the United States or Canada. The recent American College of Cardiology Foundation/American Heart Association heart failure guideline, which was published in April 2009, did not imply levosimendan (36).

Coronary artery disease

Conventional positive inotropic agents (phosphodiesterase inhibitors and adrenergic agonists such as dobutamine) increase myocardial oxygen demand and also induce myocardial ischemia or malignant ventricular tachyarrhythmias (37, 38). On the contrary, by virtue of its dual mechanism of action and its negligible effect on myocardial oxygen demand, levosimendan seems to be better tolerated by patients with ischemic heart disease (39).

In a recent double-blind, placebo-controlled study (40), 24 patients undergoing a percutaneous coronary intervention for an acute coronary syndrome were enrolled, ten minutes after percutaneous coronary intervention, the patients were randomized to either levosimendan treatment (24 µg/kg over 10 min) or placebo. Hemodynamic variables were measured before and 20 min after the start of drug infusion. Levosimendan treatment was associated with a significant reduction in the mean total number of hypokinetic segments. In addition, the pressure-volume area, end-systolic pressure, and volume index were significantly decreased. In addition, the index of diastolic relaxation decreased with levosimendan compared with placebo, indicating that levosimendan improved the systolic performance of stunned myocardium without impairment of diastolic function (40).

Cardiogenic and septic shock

There are several clinical observations indicating that levosimendan can improve hemodynamics even in patients with cardiogenic shock (CS) if it is combined with catecholamines to maintain adequate perfusion pressures (41, 42). Samimi-Fard et al. (43) investigated the effect on long-term survival of levosimendan compared to dobutamine treatment in patients with ST elevation myocardial infarction revascularized by primary coronary angioplasty who subsequently developed cardiogenic shock.

Levosimendan compared to dobutamine did not improve long-term survival in this study. Moreover, Tsagalou et al. (44) showed that hemodynamic benefit conferred by levosimendan added to catecholamines in patients with cardiogenic shock after acute myocardial infarction was limited to patients with high systemic vascular resistance.

There is an increasing evidence that levosimendan exerts beneficial effects in the treatment of sepsis-induced myocardial and pulmonary dysfunction (45, 46). Future large-scale multicenter clinical trials are needed to clarify whether levosimendan improves the overall outcome of patients with sepsis and septic shock.

Peri-operative area of cardiac surgery

Low output is a result of myocardial stunning and is common after cardiopulmonary bypass. Therefore, patients with low-output state need treatment aimed at enhancing hemodynamics and cardiac function. A recently published meta-analysis (47) investigated the effects of levosimendan in cardiac surgery. The endpoint was postoperative cardiac troponin release. Levosimendan was associated with a significant reduction in cardiac troponin peak release (weighted mean difference=2.5 ng/dL [95% CI -3.86, -1.14], p=0.0003) and in time to hospital discharge (weighted mean difference=-1.38 days [95%CI-2.78, 0.03], p=0.05). Moreover, Aksun et al. (48) emphasized importance of timing of administration of levosimendan in high-risk patients who underwent cardiovascular surgery. According to this study, levosimendan is effective in high-risk cases during cardiac surgery, especially during the intra-operative and pump removal periods; however, no successful outcomes were observed during the post-operative period.

These peri-operative and post-operative studies in adult patients indicate that levosimendan is a potentially useful drug to prevent and/or improve hemodynamics and post-operative ischemic cardiac depression.

Usage in pediatric patients

Recent trials demonstrated the safety and efficacy of this new agent during the pre- or post-operative phase in infants or children with congenital heart disease (49, 50). Turanlahti et al. (50)

assessed the pharmacokinetics, hemodynamic effects and safety of levosimendan in 13 children (from 3 months to 7-year-old) with congenital heart disease evaluated for cardiac surgery. The hemodynamic profile of levosimendan in children was similar to that in adult patients with HF without any important adverse event or unexpected adverse drug reactions. However, the improvement in hemodynamic variables was not statistically significant compared with baseline, probably because of the small dose administered relative to body surface area and limited patient size.

Right heart failure and pulmonary hypertension

Right ventricular dysfunction frequently complicates advanced left ventricular HF and contributes to an unfavorable prognosis. In animal and human clinical studies, levosimendan has been shown to improve right ventricular systolic and diastolic function, and to reduce systolic pulmonary artery pressure (51, 52). However, the potential pulmonary vasodilating effect of levosimendan in patients with idiopathic pulmonary arterial hypertension remains unclear. Çavuşoğlu et al. (53) recently published report of two cases of levosimendan use in two patients with nonvasoreactive idiopathic pulmonary arterial hypertension. Levosimendan use was accompanied with deterioration in clinical status of patients, increase of pulmonary pressures and absence of a substantial improvement of the patient's condition. Formal controlled and comparative studies are necessary to define the place of levosimendan in such patients.

Oral use of levosimendan

Limited numbers of studies have been conducted to obtain preliminary data for the development of its oral formulation (54, 55). In an open-label pilot study (55), levosimendan was administered orally to 10 patients with severe congestive HF. Each patient received three escalating doses of 1 mg, 2 mg and 4 mg of levosimendan within 18-24 h. After administration of a 1-mg dose, PCWP was decreased by 18% and cardiac output was increased by 22%. The 4-mg dose of levosimendan was associated with a 27% increase in cardiac output and right atrial pressure decreased substantially by 40% (55).

In The PERSIST study (56), 307 patients with NYHA IIIB-IV chronic HF were randomly assigned, in a double-blind fashion, to levosimendan 1 mg once or twice daily or placebo for at least 180 days. An exploratory primary end-point, a composite consisting of repeated symptom assessments, worsening HF and mortality during 60 days was used. Minnesota Living with Heart Failure Quality of Life score (MLHFQoL) and NT-proBNP were assessed repeatedly. No differences in symptoms emerged and worsening HF events and death were found, resulting in a similar Patient Journey score with levosimendan and placebo (p=0.567). Compared to placebo, an improvement of 3-4 points in MLHFQoL at several time-points in favor of the combined levosimendan groups was observed (p<0.001), which was accompanied by a substantial and persistent reduction in NT-proBNP levels (-30-40%) (p<0.001). Further research with this compound is warranted to clarify safety and efficacy.

Therapeutic use, dosage and adverse effects

Treatment with levosimendan is usually initiated with a 10 min loading bolus of 3 to 12 mcg/kg followed by a 24-hour continuous infusion of 0.05 to 0.2 mcg/kg per min. If the patient has hypotension, one should either skip the loading dose or associate norepinephrine in low doses. Adverse cardiovascular events may be seen more frequently in doses above 0.2 μg $kg^{-1}min^{-1}$. The most common adverse events related with the use of levosimendan are nausea, dizziness, headache and hypotension (57). All these adverse events are attributed to to the vasodilatory effects of this drug. In the REVIVE-2 trial, levosimendan was associated with increased incidence of hypotension and ventricular tachycardia compared to placebo (23). These adverse effects may be related to more severe disease of study population, high-sustained infusion of levosimendan and the frequent use of other intravenously active therapies. In the SURVIVE study (58), levosimendan-treated patients were less likely to experience cardiac failure (p=0.02) and more likely to experience atrial fibrillation (p=0.05), hypokalemia (p=0.02) and headache (p=0.01) compared with dobutamine-treated patients, during the initial 31 days following drug administration. The treatment groups were similar with respect to frequency of renal insufficiency, hypotension and ventricular arrhythmias. In a recent randomized open-label end- point blinded study (59), we compared the effects of levosimendan and dobutamine on ventricular arrhythmias and prognostic autonomic nervous system-related markers in patients with decompensated advanced HF. Fifty-eight patients (mean age 64 ±10 years) with HF refractory to conventional therapy and LVEF≤35% were randomized to levosimendan (n=30) or dobutamine (n=28). Time-domain indices of heart rate variability (HRV) and QTc were obtained from 24-hour Holter recordings immediately before and during drugs therapy. Echocardiography and BNP measurements were also performed at baseline and after treatment. Dobutamine significantly increased heart rate (6.8±4.2 per minute, p<0.01), episodes of nonsustained ventricular tachycardia (from 3.2±1.6 to 20.4±9.2, p<0.05) and QTc (from 406±41 msec to 426±34 msec, p<0.05). Dobutamine therapy also resulted in a decrease in standard deviation of the R-R intervals over a 24-hour period (SDNN), standard deviation of all 5-minute mean R-R intervals (SDANN), and the percentage of R-R intervals with >50ms variation (pNN50) (all p<0.05). Levosimendan did not affect these variables. Our findings demonstrated that dobutamine was associated with substantial proarrhythmic and chronotropic effects in patients with advanced HF. Furthermore, dobutamine can potentially lead to further deterioration of autonomic dysregulation. Levosimendan group showed a greater improvement in neurohormonal activation compared to dobutamine group, although, it had a neutral effect on prognostic autonomic nervous system-related markers. Therefore, levosimendan may have better safety for short-term treatment of these patients (58).

Serum creatinine levels were affected positively even among the patients with baseline renal failure (60). In a recent study with an in vitro model reported that levosimendan had a significant inhibitory effect on platelets in clinically relevant doses (61).

Conclusion

Levosimendan is a new promising inotropic agent for therapy of advanced HF. It has more favorable effects regarding improvement of HF symptoms, neurohormonal activation and hemody-

namics compared to conventional positive inotropic agents. The overall experience with levosimendan suggests that despite its positive inotropic action, it may not be associated with excess mortality. Moreover, it may decrease mortality, especially in patients with BNP reduction during treatment for acute HF. Nonetheless, these beneficial effects seem to be balanced by the higher incidence of cardiac side effects in critically ill patients who are under aggressive management with other vasoactive agents, when compared to placebo. Levosimendan may be used instead of dobutamine in patients with low cardiac output and high LV filling pressures not responding to other therapies. Larger randomized, placebo-controlled, clinical trials focused on patients with severe acute HF are warranted before making any definitive recommendation.

Conflict of interest: None declared

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