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META-ANALYSIS

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Repetitive Infusion of Levosimendan in Patients with Chronic Heart Failure: A Meta-Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Repetitive or intermittent levosimendan infusion is gradually becoming more commonly considered for patients with advanced chronic heart failure. However, previous randomized controlled studies (RCTs) reported conflicting results on the effects of levosimendan when administered repetitively. The aim of this meta-analysis was to generate up-to-date evidence to assess the effect of levosimendan in this group of patients.

Material/Methods: A literature review identified 8 qualified studies. A meta-analysis was performed to assess mortality and left ventricular ejection fraction (LVEF).

Results: Use of levosimendan contributed to significantly reduced mortality at the end of mid-term follow-up. The mortality rates in levosimendan and control group were 23 of 226 (10.2%) and 53 of 198 (26.8%), respectively (RR: 0.40, 95%CI: 0.26–0.63, P<0.0001). The trend of significantly decreased mortality was observed in levosimendan *vs.* placebo subgroup (RR: 0.28, 95%CI: 0.15–0.54, P=0.0001, I^2=0%) but not in levosimendan *vs.* dobutamine, PGE1, or furosemide subgroup (p=0.19, p=0.64 and p=0.25, respectively). Levosimendan also contributed to significantly improved LVEF improvement at the end of follow-up (mean difference: 3.69%, 95CI: 0.92–6.45%, p=0.009).

Conclusions: Intermittent or repetitive levosimendan infusion might be a promising strategy to reduce mortality and improve LVEF in patients with advanced chronic, but not necessarily acutely decompensated, heart failure to maintain disease stability.

MeSH Keywords: Heart Failure • Meta-Analysis • Treatment Outcome

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Background

Beta-blockers have been demonstrated to be reliable medication for patients with heart failure (HF) and are currently used as first-line treatment in combination with angiotensin-converting enzyme (ACE) inhibitors [1,2]. Although the administration of combined beta-blockers and ACE inhibitors may bring some benefits for this group of patients, chronic heart failure might still be progressive, and a large proportion of the patients eventually develop decompensation. Therefore, these patients may need inotropic agents to improve hemodynamics. Intravenous infusion of inotropes is widely applied as a practice to get more definitive measures or as palliative treatment for decompensation of chronic heart failure [3]. A single administration is insufficient to generate long-lasting results and affect outcome [4]. However, intermittent or continuous treatment of chronic heart failure with intravenous inotropes might increase the risk of proarrhythmic effects and subsequent mortality [5].

Levosimendan is an inotropic agent stabilizing the open conformation of troponin C and the troponin C -calcium-tropomyosin complex and enhancing calcium sensitivity of cardiac myofilaments [6]. However, unlike other positive inotropic agents, the effect of levosimendan is not dependent on cellular calcium intake or intracellular ionized calcium concentration [7]. Therefore, this agent does not impair ventricular relaxation and does not cause intracellular calcium overload and associated arrhythmias. In addition, levosimendan can also lead to vasodilatation through opening adenosine triphosphate-dependent potassium channels [8]. Therefore, based on the inotropic and vasodilatory functions, levosimendan can result in increased cardiac output, without excessive myocardial oxygen demand [9,10]. Due to this benefit, this agent is considered for repetitive or intermittent use in patients with advanced chronic heart failure [11]. However, previous RCTs reported conflicting results in the effects of levosimendan when administered repetitively. The aim of this meta-analysis was to generate up-to-date evidence to assess the effect of levosimendan in this group of patients.

Material and Methods

Search strategy

Relevant studies were searched in PubMed, MEDLINE, Cochrane Library, and ClinicalTrials.com from Jan 1995 to May 2014 by 2 authors independently (YGY and LJX). The whole search was based on the following terms and strategy: ("levosimendan" OR "simdax") AND ("chronic" OR "congestive") AND ("heart failure" OR "HF") AND ("repetitive" OR "Intermittent" OR "continuous") AND ("randomized controlled trial" OR "RCT" OR "clinical trial" OR "trial"). No language restriction was set during searching. To ensure all qualified studies were included, backward snowballing method was performed by manual screening of introduction and reference list of included studies, relevant meta-analysis, and reviews.

Study selection and selection criteria

Studies meeting the following include criteria at the same time were included in this meta-analysis: (1) randomized controlled trial; (2) recruited patients with advanced chronic heart failure; (3) had at least 2 arms comparing intermittent use of levosimendan and control group (other agents/best available treatment/placebo); (4) efficacy outcomes, such as mortality, could be extracted from original studies; (5) duration of follow-up lasted at least 1 month. Studies meeting any of the following criteria were excluded: (1) oral administration of levosimendan; (2) non-adult studies; (3) incomplete or lack of required data. Two authors performed screening and selection independently. Divergences were resolved by group discussion with a third author by referring to original studies.

Data extraction, study quality, and bias assessment

The following information about basic characteristics of a study were extracted: last name of the first author, year of publication, regime of intervention and control group, number of patients in each group, dose and duration of agent administrated, lapse, and duration of follow-up. Outcome data extracted for efficacy analysis mainly included mortality at the end of follow-up and left ventricular ejection fraction (LVEF) improvement. Quality of the included RCTs was assessed by methodological quality item of RCT according to the Cochrane Handbook for Systematic Reviews of Interventions. Internal validity and publication bias were assessed by Cochrane Collection methods. Publication bias was assessed by visually inspecting funnel plots.

Data synthesis and analysis

All data synthesis and analysis in this study were performed using RevMan 5.2 software (Cochrane Collaboration). Discontinuous outcome (mortality) and continuous outcome (LVEF) from individual studies were extracted and pooled to make estimate of risk ratios (RR) and corresponding 95% confidence intervals (CIs). Between-studies heterogeneity was measured with the chi-square-based Q test and I^2. $P<0.1$ or $I^2>50\%$ was considered as significant heterogeneity. A primary analysis was conducted with a fixed-effects model. If $I^2 \leq 50\%$ and $p \geq 0.1$, a fixed-effects model with Mantel-Haenszel method was used to make estimates, otherwise a random-effects model was used. The significance of pooled estimates was assessed with the Z test and $p<0.05$ was considered as a statistically significant difference.

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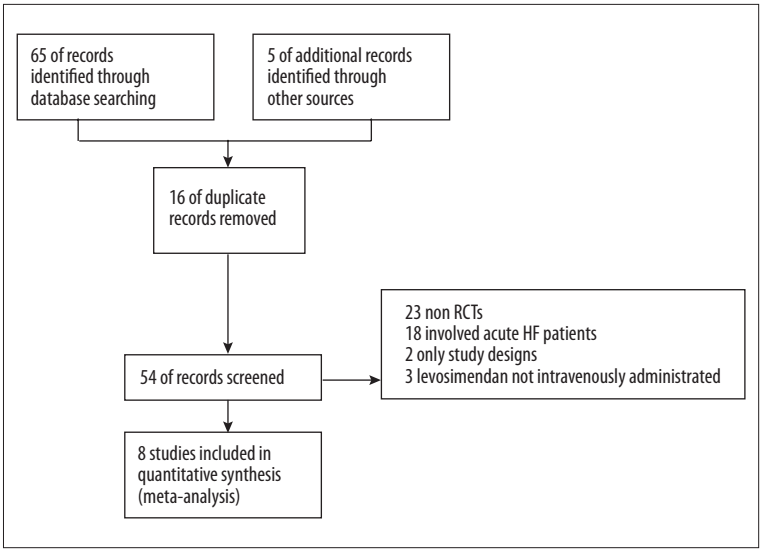

Figure 1. The searching and screening process.

Table 1. The key characteristics of trials included.

Study	No Pts		Levo bolus (μg/kg)	Levo infusion (μg/(kg·min))	Duration Levo (h)	Lapse	Control agent	Follow up (d)
	Levo	Control						
Altenberger 2014	63	57	0	0.2	6	Bi-weekly	Placebo	26 wks
Bonios 2012	21	21	0	0.3	6	Weekly	Dobu	6 m
Berger 2007	39	36	12	0.1	24	Monthly	PGE1	12 m
Levin 2009	40	40	0	0.1	24	Bi-monthly	Placebo	12 m
Malfatto 2012	22	11	0	0.1–0.4	24	Monthly	Furosemide	16 m
Mavrogeni 2007	25	25	6	0.1–0.2	24	Monthly	Placebo	6 m
Kleber 2009	18	10	12	0.2	23	Bi-weekly	Placebo	12 wks
Parissis 2006	17	8	6	0.1–0.4	24	3 weekly	Placebo	114 d

Levo – levosimendan; Dobu – dobutamine; No. Pts – number of patients; PGE1 – prostaglandin E1; wks – weeks; m – month; d – day.

Results

Characteristics of studies included

Through a search of databases, a total of 8 studies were finally included in this meta-analysis. The whole search process is briefly described in Figure 1. Among the 8 studies included, 5 compared levosimendan *vs.* placebo [12–16]; 1 compared levosimendan *vs.* dobutamine [17]; 1 compared levosimendan *vs.* furosemide[18], and 1 compared levosimendan *vs.* prostaglandin E1 (PGE1) [19]. The 8 studies involved 453 patients in total, with 245 in levosimendan groups and 208 in control groups. The basic characteristics of the trails are summarized in Table 1. Seven studies reported mid-term mortality, but the study by Parissis et al. [15] did not. All patients in these trials were recruited in cardiological settings, defined as heart failure caused by heart diseases except cardiac surgery. Four studies applied a continuous infusion of levosimendan without the bolus dose [12,16–18]. Dose of continuous infusion ranged from 0.1 to 0.4 μg/kg/min. Follow-up ranged from 114 days to 16 months. The intervals of administration were weekly, every 2 weeks, every 3 weeks, monthly, and every 2 months. Therefore, the clinical heterogeneity was largely related to dose, control treatment, and follow-up duration. Quality assessment showed that 5 studies had a moderate risk of bias [13,14,16,18,19] and 3 had a low risk of bias [12,15,17].

Mid-term mortality

The mid-term mortality reported by 7 trials was pooled in Figure 2. Due to no between-studies heterogeneity observed (I^2=0%), a fixed-effects model was used. Generally, use of levosimendan contributed to significantly reduced mortality at the end of follow-up. The mortality rates in levosimendan and

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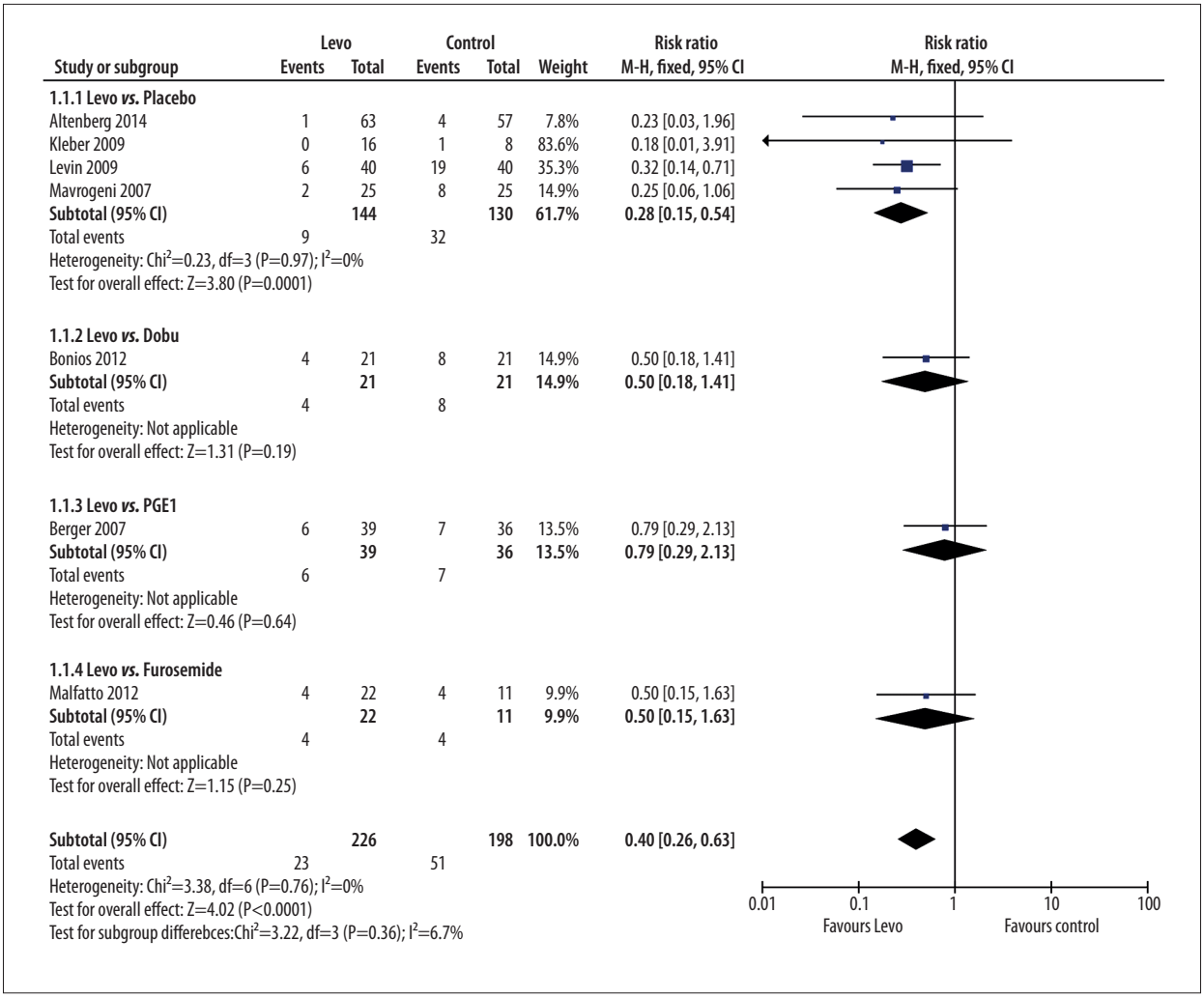

Figure 2. Meta-analysis of mortality rate at the end of follow-up.

control groups were 23 of 226 (10.2%) and 53 of 198 (26.8%), respectively (RR: 0.40, 95%CI: 0.26–0.63, P<0.0001) (Figure 2). Due to heterogeneous agents used in the control group, subgroup analysis was also performed. The trend of significantly decreased mortality was observed in levosimendan *vs.* placebo subgroups (RR: 0.28, 95%CI: 0.15–0.54, P=0.0001, I^2=0%) (Figure 2). However, in levosimendan *vs.* dobutamine, PGE1, or furosemide subgroups, no significant difference was observed (p=0.19, p=0.64 and p=0.25, respectively) (Figure 2). In comparison to dobutamine, furosemide, or PGE1, there was only 1 study that included in each subgroup. Funnel plot analysis showed that the mid-term mortality outcomes of the 7 trials had symmetric distribution, suggesting there was no publication bias (Figure 3).

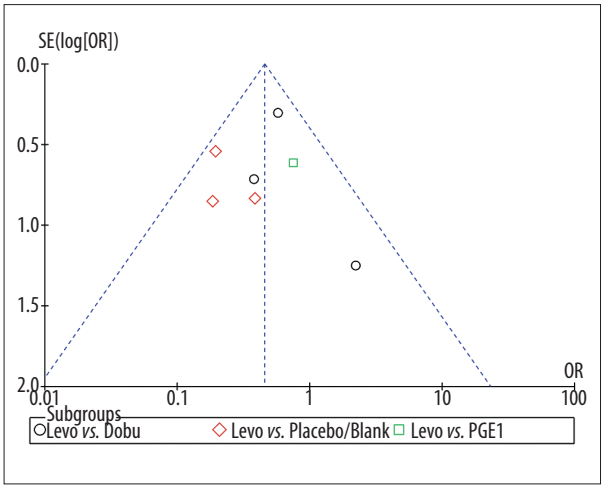

Figure 3. Funnel plot analysis of the mid-term mortality outcomes.

Left ventricular ejection fraction (LVEF) improvement

Five studies have reported LVEF improvement data in both intervention and control groups during the whole follow-up period.

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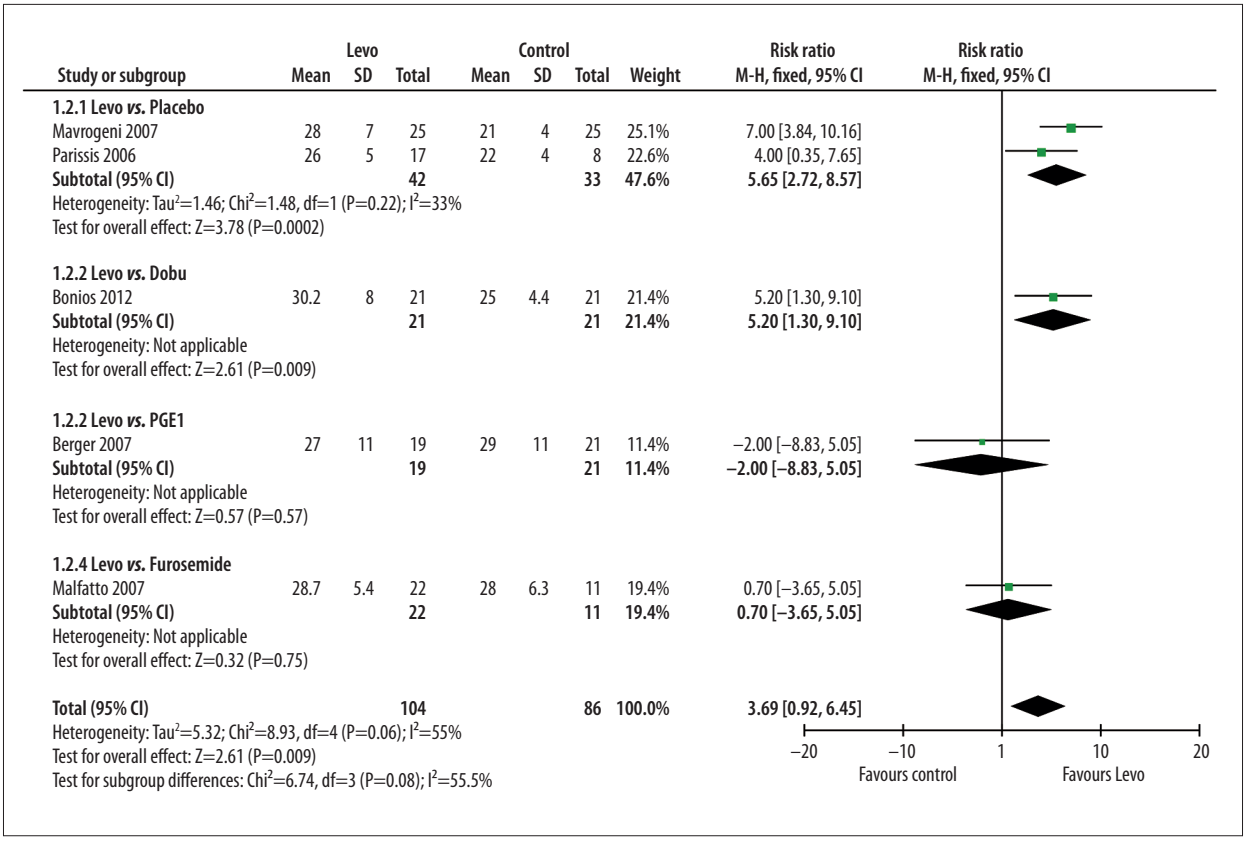

Figure 4. Meta-analysis of LVEF comparisons at the end of follow-up.

Due to significant heterogeneity observed (I^2=55%), a random-effects model was used. Pooled results showed that use of levosimendan contributed to significantly improved LVEF at the end of follow-up (mean difference: 3.69%, 95CI: 0.92–6.45%, p=0.009, I^2=55%) (Figure 4). Similar to mid-term mortality, subgroup analysis showed that LVEF improvement was quite significant in levosimendan *vs.* placebo subgroups (mean difference: 5.65%, 95%CI: 2.72–8.57%, P=0.0002, I^2=33%) (Figure 4). Compared with dobutamine, levosimendan was also associated with significant LVEF improvement (p=0.009). However, in levosimendan *vs.* furosemide or PGE1 subgroup, no significant difference was observed (p=0.75 and p=0.57 respectively) (Figure 4). In comparison to dobutamine, furosemide, or PGE1, there was only 1 study included in each subgroup.

Discussion

Two recent meta-analyses also assessed the use of levosimendan in chronic advanced heart failure patients [11,20]. However, these 2 studies simply pooled all studies with different control arms into 1 group. This method is prone to generate significant heterogeneity and also failed to evaluate the difference in comparisons with different control arms. In the current study, stratified analysis was performed to make overall estimation of all studies and to compare therapeutic effect difference with different control arm at the same time. Our findings provided updated evidence about the effect of repetitive administration of levosimendan in chronic advanced heart failure patients and found the use of levosimendan is associated with a significant reduced mortality risk in mid-term follow-up and improved LVEF in a cardiologic setting. However, the effect is generally more evident when compared with placebo, rather than dobutamine, PGE1, or furosemide.

For patients with end-stage chronic heart failure, prognosis is always poor. Long-term mechanical circulatory support or heart transplantation could significantly improve prognosis. However, limited availability of assist devices and donor heart, lack of professional expertise, and high cost make these choices impossible for a large proportion of the patients [21]. Although inotrope therapy could provide improvement in hemodynamic function, long-term and intermittent use of inotropic agents is not recommended for patients in current treatment guidelines [3]. At present there is no large randomized, placebo-controlled trial that has assessed the efficacy of intermittent intravenous inotropes for decompensated end-stage chronic heart failure.

The SURVIVE study compared the efficacy and safety of levosimendan *vs.* dobutamine for patients with acute heart failure

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in a cardiological setting. Although this study found that short-term infusion of levosimendan had no obvious benefits over dobutamine in all-cause mortality at 180 days or any other secondary clinical outcomes [22], the effect of continuous use is still not well defined and the unique pharmacokinetic features of levosimendan make it an ideal agent for intermittent weekly infusions. The positive inotropic effects of levosimendan is mainly related to its effect on to troponin C and calcium, stabilizing conformational change of tropomyosin molecule, and prolonging tropomyosin contraction through enhancing actin-myosin overlap, without increasing the concentration of intracellular calcium [23]. The half-life of this agent is about 1 h and its active metabolite OR-1896, which had similar pharmacologic properties as the original agent, has a half-life of 80–90 h [23]. Thus, with a single intravenous administration, the hemodynamic effects of hemodynamic effects can last 1 to 2 weeks [24]. Therefore, intermittent use of levosimendan might bring even longer-term benefits for the patients. According to a previous study, levosimendan is helpful to improve cardiac function or even generate favorable reverse cardiac remodeling through activation of pro-inflammatory cytokines and the deleterious neurohormonal systems [25]. Actually, Parissis et al. observed that levosimendan infusion contributed to significant decrease in plasma N-terminal-pro BNP and interleukin 6, through which to active neurohormonal and immune responses [15].

According to the recommendation of the European guidelines for diagnosis and treatment of acute and chronic heart failure [26], inotropic agents could be considered for acute or chronic heart failure patients with hypoperfusion and/or hypotension to increase blood pressure and cardiac output, and to improve peripheral perfusion. However, due to the possible negative arrhythmias and myocardial ischemic effects, electrocardiogram should be monitored continuously. Levosimendan is classified as a class IIa recommendation. It is a unique agent, different from other inotropic agents since its positive inotropic effects do not need excessive myocardial oxygen consumption [23]. Therefore, it did not increase workload of the heart. β-adrenergic agonist or PDE inhibitors can all cause complications such as myocardial injury, ischemia, and arrhythmia. Although some studies reported that levosimendan presented PDE-III inhibitor effects at higher concentrations (>0.3 μm), it does not cause these complications in the clinically recommended therapeutic range (0.03–0.3 μM or 10–100 ng/mL) and mainly acts as a Ca^{2+} sensitizer at the recommended concentration range [27]. Actually, in a recent expert panel consensus, 30 experts from 15 countries agreed that intermittent or repetitive levosimendan could be considered for patients with advanced chronic, but not necessarily acutely decompensated, heart failure to maintain disease stability [12]. Therefore, levosimendan might be a promising agent for this group of patients.

This study also has several limitations. Firstly, the number of trails and the number of patients in each trial is relatively small. Secondly, the experimental arm of included studies had heterogeneity in the dose and the interval of levosimendan administration, while the control arm had heterogeneity in agents used. Therefore, this study made subgroup analysis to separate different control agents. However, due to the limited number of original studies, the number of patients in each subgroup is small, which weakened the statistical power of the findings. Thirdly, the follow-up of included trials was relatively short. The long-term effects of serial levosimendan infusions are still not quite clear. Therefore, in the future, large RCTs with long-term follow-up are required to assess levosimendan as a part of standard therapy for chronic heart failure. Currently, there are 3 on-going studies assessing the use of levosimendan in advanced chronic heart failure patients (NCT01536132, NCT00988806, and NCT01290146). In the near future, we can expect more solid evidence.

Conclusions

Intermittent or repetitive levosimendan infusion might be a promising strategy to reduce mortality and improve LVEF for patients with advanced chronic, but not necessarily acutely decompensated, heart failure to maintain disease stability.

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