Levosimendan in Patients with Left Heart Failure After Acute Myocardial Infarction - Review of the RUSSLAN Study and Future Developments with Levosimendan

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Summary

The RUSSLAN study was designed as a randomised, placebo-controlled, double blind study to evaluate the safety and efficacy of levosimendan in patients with left ventricular failure due to acute myocardial infarction (AMI). This study was performed in several university centers and included 504 patients, who were given a bolus followed by i.v. infusion of levosimendan in different dose groups (0.1–0.4 µg/kg/min) or placebo for 6 hours if tolerated.

The incidence of hypotension and ischaemia was similar in all groups (p = 0.319). Only in the highest levosimendan dose group the observed incidence of ischaemia or hypotension was higher. The risk of death and worsening of heart failure was lower in levosimendan than in placebo treated patients both during the 6-hour infusion period (2.0 % vs. 5.9 %; p = 0.033) and over 24 hours (4.0 % vs. 8.8 %; p = 0.044). Levosimendan treated patients had a significantly lower mortality rate compared to placebo treated patients during the first 14 days (11.7 % vs. 19.6 %; hazard ratio 0.56 [95 % CI 0.33–0.96]; p = 0.031). The positive effect was maintained during the 180-day follow-up (22.6 % vs. 31.4 %; 0.67 [95 % CI 0.45–1.00]; p = 0.053).

Levosimendan doses (0.1–0.2 µg/kg/min) did not induce hypotension nor ischaemia, but reduced the risk of worsening heart failure and death in patients with LVF due AMI.

Introduction

Levosimendan, the first of a new class of calcium sensitisers, has been introduced into clinical practice for the treatment of acutely decompensated, severe heart failure. By virtue of its dual mechanism of action, levosimendan (1) enhances cardiac contractility through myofilament calcium sensitisation [1] and (2) induces peripheral and coronary vasodilation by opening ATP-sensitive potassium channels [2].

Levosimendan binds to troponin-C [3], thereby sensitising the contractile proteins to intracellular calcium without increasing the influx of calcium into the cardiac myocytes [4]. As a result, cardiac performance is improved with no increase in oxygen consumption [5]. In contrast to other agents with calcium-sensitising properties, the effects of levosimendan are calcium-dependent, facilitating normal diastolic relaxation [6]. Moreover, by mediating both arterial and venous dilatation, levosimendan reduces both cardiac preload and afterload [7, 8].

The prognosis of patients with acute myocardial infarction (AMI) complicated with heart failure is poor despite current standard therapy. The annual mortality rate is 20–40 % [9–11]. To date, clinical studies have demonstrated the efficacy and good tolerability of levosimendan in over 1000 patients with acute decompensated heart failure of both ischaemic and non-ischaemic origin [7, 8, 12, 13]. Favourable haemodynamic effects and symptomatic improvement are accompanied by no increase in mortality up to 6 months after the decompensating event compared with dobutamine [14].

The objective of the RUSSLAN [13] (Randomised stUdy on Safety and effectivenesS of Levosimendan in patients with left ventricular failure due to an Acute myocardial iNfarct) study was to evaluate the short- and long-term safety and efficacy of a 6-hour infusion of levosimendan in patients with left ventricular failure (LVF) complicating an AMI.

Methods

The levosimendan efficacy and safety trial in myocardial infarct patients was a placebo-controlled, double-blind, parallel-group, randomised trial. 504 patients were recruited within 5 days after AMI (mean about 2 days). The patients were required to have evidence of LVF on chest X-ray and clinical need for inotropic therapy.

Levosimendan was administered as indicated in Fig. 1 with a 10 min bolus followed by a continuous infusion for a total of 6 hours.

The primary end-point was the proportion of patients developing clinically significant hypotension and/or myocardial ischaemia adjudicated by an independent safety committee. Hypotension was evaluated on the basis of symptoms or a decrease in systolic blood pressure, and myocardial ischaemia was evaluated on the basis of occurrence of chest pain or ECG changes.

Secondary variables comprised risk of death or worsening heart failure during 24 hours, and all-cause mortality during
14 days. The mortality follow-up was retrospectively extended to 180 days.

**Results**

Baseline characteristics and concomitant medications were similar in all treatment groups, albeit more patients with diabetes were treated with levosimendan than placebo. The patients used following baseline and concomitant medication: 94–98 % nitrates, 45–49 % ACE inhibitors, 32–42 % betablockers, 86–90 % acetylsalicylic acid, 14–22 % thrombolytic therapy, 70–76 % diuretics.

The proportions of patients who experienced ischaemia and/or hypotension in the placebo and combined all four levosimendan groups was similar (10.8 % vs. 13.4 %, respectively; p = 0.456). Although there was a weak correlation between the dose of levosimendan and the risk of hypotension and/or ischaemia (p = 0.054), this was totally attributable to the higher frequency observed with the highest dose (19 % compared with 11–12 % in the other levosimendan and placebo groups).

The combined risk of death and worsening heart failure was significantly lower in patients treated with levosimendan than in patients treated with placebo, both during the 6-hour infusion period (2.0 % vs. 5.9 %, respectively; p = 0.033), and at 24 hours (4.0 % vs. 8.8 %, respectively; p = 0.044).

Levosimendan-treated patients had significantly lower all-cause mortality than placebo-treated patients during the 14-day follow-up period (11.7 % vs. 19.6 %, respectively; p = 0.031). The positive effect on mortality was maintained over the 180-day follow-up (22.6 % vs. 31.4 %, respectively; p = 0.053) (Fig. 2). The reduction in mortality attributable to levosimendan was achieved during the first 14 days, since after 14 days the Kaplan-Meier curves remain parallel. There was no relationship between the dose of levosimendan and all-cause mortality (Fig. 3).

There were few significant differences in adverse events between levosimendan and placebo. Myocardial rupture occurred more frequently with placebo; sinus tachycardia was more common in patients receiving the highest dose of levosimendan.

**Conclusions**

Levosimendan dosing with bolus 6–12 µg/kg followed by infusion 0.1–0.2 µg/kg/min correspondingly was safely administered and did not increase clinically significant hypotension or myocardial ischaemia compared with placebo. Levosimendan significantly reduced in-hospital mortality compared with placebo, with a long-term survival benefit lasting up to 180 days. Worsening heart failure and death was significantly reduced in levosimendan treated patients during the first 24 hours. Levosimendan was a well-tolerated and effective treatment in patients with LVF complicating AMI, even without invasive monitoring.

**Future Developments**

The future development program of levosimendan comprises mainly of two large scale trials in patients with decompensated heart failure. One placebo-controlled trial is currently conducted in the USA and the other active-control study is in planning phase to be initiated in Europe early in 2003. The US phase III study morbidity trial is estimated to be completed in the 2nd quarter of 2004. The European study will be probably looking at the effect of levosimendan on mortality.

Other areas, like the effect of LS in pulmonary hypertension and repeated dosing will be explored. The role of levosimendan in postoperative heart failure patients will be also investigated more thoroughly.

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References:

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