

Is there a place for levosimendan in the intensive care unit?

Anthony Delaney, Celia Bradford, John McCaffrey,
Sean M Bagshaw and Richard Lee

Levosimendan is a novel calcium-sensitising agent. Its basic pharmacology and results of early clinical trials have been well documented.^{1,2} It has been proposed as a potentially valuable treatment of acute or decompensated severe heart failure,³ and it is in this context that levosimendan would most commonly be prescribed in the intensive care unit. Early clinical trials described some improvements in haemodynamic parameters and suggested there may be a survival benefit. However, before concluding that there is a place for the routine use of levosimendan in the ICU, all the available evidence needs to be carefully appraised.

Framework for assessing the evidence

When clinicians are assessing the evidence regarding the efficacy of levosimendan, a few factors need to be considered.

Firstly, there are important pharmacological factors. Levosimendan has an active metabolite, OR-1896, which has a similar positive inotropic effect to the parent compound.⁴ This metabolite has a half-life of 80–96 hours and exerts a clinical effect for about a week. Thus, levosimendan given as a 24-hour infusion has a clinical effect that may last up to 7–10 days. To conclude that it is superior to comparable therapy, the comparator would need to be given in such a way that it is active for a similar period.

Secondly, methodological issues need to be taken into account when appraising the evidence. It is well known that the use of surrogate outcomes can be misleading, and definitive clinically meaningful end-points, such as mortality, are preferable.⁵ It is also well described that the results of early trials often differ from the results of later, more definitive trials.⁶ Clinical trials that are stopped early because they have shown benefit may be misleading and conclude a benefit when there is none, or overestimate the treatment effect.⁷ It is also essential that appropriate statistical analysis is used to adjudicate the role of chance in the results of any clinical trial. Overall, the best evidence for assessing whether levosimendan has a role in the ICU should come from adequately powered and methodologically sound randomised clinical trials.⁸ Clinicians should keep these methodological issues in mind when assessing the evidence put forward to support the use of levosimendan in patients with acute severe heart failure.

Initial clinical studies

A number of uncontrolled clinical studies have demonstrated improvements in haemodynamic end-points with the use of

ABSTRACT

Introduction: Levosimendan is a novel calcium-sensitising agent that has been proposed as a potentially valuable inotrope for the treatment of acute or decompensated severe heart failure. Early clinical trials described some improvements in surrogate haemodynamic parameters, and suggested a possible survival benefit. However, before concluding that there is a place for routine use of levosimendan in the intensive care unit, a careful appraisal of all available evidence is needed.

The evidence: Two phase II clinical trials, RUSLAN and LIDO, have shown reduced mortality when levosimendan was compared with placebo and dobutamine, respectively. The CASINO study, yet to be fully reported, also purports to show a beneficial effect of levosimendan. In contrast, the two largest studies, REVIVE and SURVIVE — also yet to be fully reported — show no effect of levosimendan.

Conclusions: The best available evidence comes from the two large clinical trials, REVIVE and SURVIVE. These studies suggest that levosimendan does not improve survival for patients with acute severe heart failure. Until their results can be fully scrutinised, and placed in the context of all available evidence, we should conclude that there is no place for levosimendan in the ICU.

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levosimendan.¹ However, improvements in such surrogate outcomes alone cannot make the case for its widespread use. Claiming that levosimendan must be useful because it causes a modest reduction in pulmonary artery occlusion pressure is analogous to claiming that antiarrhythmic drugs must be beneficial because they reduce ventricular ectopy. The folly of this type of reasoning has been well documented.⁹

Proponents of the use of levosimendan typically cite two early clinical studies to support the case for its use in acute severe heart failure.^{10,11} RUSLAN (Randomised sTudy on Safety and effectiveness of Levosimendan in patients with left ventricular failure due to an Acute myocardial iNfarct)¹¹ showed that it is possible to find an acronym in any study title. This study of 504 patients with left ventricular failure complicating acute myocardial infarction compared four different doses of levosimendan and placebo given over 6 hours. Results showed levosimendan-treated patients had lower 180-day mortality than patients treated with placebo (22.6%

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v 31.4%; hazard ratio (HR), 0.67; 95% CI, 0.45–1.0; $P=0.053$). The LIDO (efficacy and safety of intravenous Levosimendan compared with Dobutamine in severe low-Output heart failure) study¹⁰ compared levosimendan (24 µg/kg bolus followed by an infusion of 0.1 µg/kg per min for 24 hours) with dobutamine (5–10 µg/kg per min for 24 hours) in 203 patients who were admitted with low output heart failure and were considered by the treating clinician to require inotropic support and invasive haemodynamic monitoring. At 6 months, mortality was significantly lower in those receiving levosimendan compared with dobutamine (26% v 38%; HR, 0.57; 95% CI, 0.34–0.95; $P=0.03$).

These two studies suggest that levosimendan may provide a survival benefit for patients with severe heart failure, but they are far from conclusive. First, we know that the results of early studies are often refuted by later studies.⁶ Second, both these studies were designed and powered to look at haemodynamic end-points. For example, the RUSSLAN study¹¹ used clinically significant hypotension or myocardial ischaemia, whereas the LIDO study¹⁰ evaluated haemodynamic improvement, defined as a 30% increase in cardiac output and a 25% fall in pulmonary capillary wedge pressure. Studies that rely primarily on surrogate end-points to determine efficacy and guide clinical practice are often unreliable.⁵ As these studies are really underpowered to detect meaningful differences in clinically important outcomes, such as mortality, they may be considered as trials that have been stopped early for benefit, a practice that again is known to be associated with an overestimate of the actual treatment effect.⁷

Finally, there are some interesting aspects to the statistical analysis performed in these trials. Both used a time-to-event analysis to ascribe a survival benefit with levosimendan. For example, the LIDO study used a survival analysis to make the case that levosimendan reduces mortality at 6 months. It appears that the follow-up at this point is complete from the Kaplan–Meier curve presented. When these same data are analysed using a conventional test for a difference in the proportions surviving, the results are slightly different. Using Fisher's exact test, the estimate of the relative risk (RR) of death is 0.69 (95% CI, 0.46–1.04; $P=0.09$). This result taken together with the result of the survival analysis implies that we cannot be sure whether more people survive when given levosimendan, or rather whether those who die take longer to do so.

The overall message that could be taken from these early studies is that levosimendan is a promising new therapy for the treatment of acute severe heart failure, but that further large-scale, methodologically rigorous studies looking at clinically important outcomes are needed. Such studies have been undertaken.

Recent clinical trials

There have been at least three large-scale clinical trials to examine the effectiveness of levosimendan for the treatment

of acute severe heart failure. While the full details of each trial are yet to be reported in peer-reviewed journals, there is sufficient information to make some preliminary observations.

CASINO

The CASINO (CALcium Sensitizer or Inotrope or NOne) study compared levosimendan (16 µg/kg bolus followed by 0.2 µg/kg per min for 24 hours) to dobutamine (10 µg/kg per min for 24 hours) and placebo in hospitalised patients with New York Heart Association class IV heart failure and a left ventricular ejection fraction (LVEF) $\leq 35\%$. This study, which was presented at the 2004 scientific meeting of the American College of Cardiology,¹² has yet to be reported fully in a peer-reviewed journal, but the main results have now appeared in a number of publications.^{1,13,14} CASINO was stopped after enrolment of 299 patients (it was planned to include 600), when levosimendan was judged to be significantly more efficacious than dobutamine or placebo. The 6-month mortality was 18% for levosimendan, compared with 28.3% in those who received placebo, and 42% in those who received dobutamine.¹⁴ This is a remarkably high mortality rate in the dobutamine group, the cause of which is not clear in the limited reports of the trial currently available.

REVIVE

The REVIVE (Randomised multicentre EVALuation of Intravenous levosimendan efficacy VERSus placebo in the short term treatment of decompensated heart failure) study^{15,16} was designed to determine the effect of levosimendan on symptoms and 6-month mortality in patients with acute decompensated heart failure. Six hundred patients admitted to hospital with acute heart failure and LVEF $< 35\%$ were randomised to an infusion of levosimendan for 24 hours or placebo. Patients requiring ventilatory support, and those with hypotension or a serum creatinine concentration $> 450 \mu\text{mol/L}$ (ie, those most likely to require ICU treatment) were excluded. While the study found a modest (6%) decrease in symptoms for those treated with levosimendan, there was no reduction in mortality — at 90 days, there were 45 deaths in the levosimendan group, and 35 in the placebo group.¹⁵

SURVIVE

The SURVIVE (survival of patients with acute heart failure in need of inotropic support) study compared levosimendan to dobutamine in patients admitted to hospital with acute heart failure and LVEF $< 30\%$.^{15,17} Levosimendan was given as an infusion for 24 hours, and dobutamine at a minimum dose of 5 µg/kg per min for a minimum of 24 hours. The primary study outcome was all-cause mortality at 180 days. A total of 1327 patients were randomised (mean age, 67 years; 72% were male; and mean LVEF, 24%). The primary analysis showed no reduction in mortality with levosimendan com-

pared with placebo (26.1% v 27.9%; RR, 0.93; 95% CI, 0.78–1.11; $P=0.46$).

While it is premature to draw strong conclusions from studies that have yet to be scrutinised in full, there are some important preliminary observations from these studies. Firstly, the results of the CASINO study must be viewed with some scepticism, given the high mortality rate in the dobutamine group. Moreover, the fact that the trial was stopped early gives rise to the suspicion that this result is at least questionable.⁷ The other two large studies, which have acronyms that do not seem to accord with their results,¹⁸ appear methodologically sound as far as can be ascertained from the information currently available, and show no benefit in terms of reduced mortality. These results cast doubt that levosimendan will prove to be an agent of great value in the ICU management of patients with acute severe heart failure.

Conclusions

The best evidence for guiding clinical practice comes from large, well designed, randomised clinical trials that measure clinically meaningful outcomes. Small trials, trials that are stopped early, and trials that rely on surrogate end-points provide much less reliable evidence that a treatment is effective. These factors need to be taken into consideration when assessing whether levosimendan has a place in the ICU.

The scenario in which levosimendan is most likely to be considered for use in the ICU is in the management of patients with acute severe heart failure requiring inotropic support. A number of small clinical trials that were designed primarily to assess the effect of levosimendan on haemodynamic markers—RUSSLAN,¹¹ LIDO¹⁰ and CASINO¹⁴—have demonstrated a modest reduction in overall mortality. These results were not confirmed in subsequent larger clinical studies—REVIVE and SURVIVE.¹⁵

Thus, the best evidence currently available suggests that levosimendan does not improve survival for patients with acute severe heart failure. Until the results of the REVIVE and SURVIVE studies can be fully scrutinised and placed in the context of all the available evidence in a high quality systematic review, we should conclude that there is no place for levosimendan in the ICU.

Author details

Anthony Delaney, Senior Lecturer,¹ and Staff Specialist²

Celia Bradford, Lecturer,¹ and Staff Specialist²

John McCaffrey, Senior Registrar²

Sean M Bagshaw, Assistant Professor,³ and Intensivist⁴

Richard Lee, Senior Lecturer,¹ and Senior Staff Specialist²

1 Northern Clinical School, Faculty of Medicine, University of Sydney, Sydney, NSW.

2 Department of Intensive Care Medicine, Royal North Shore Hospital, Sydney, NSW.

3 Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada.

4 Division of Critical Care Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada.

Correspondence: adelaney@med.usyd.edu.au

References

- De Luca L, Colucci WS, Nieminen MS, et al. Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* 2006; 27: 1908-20.
- Lehtonen L, Poder P. The utility of levosimendan in the treatment of heart failure. *Ann Med* 2007; 39: 2-17.
- Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 384-416.
- Toller WG, Stranz C. Levosimendan, a new inotropic and vasodilator agent. *Anesthesiology* 2006; 104: 556-69.
- D'Agostino RB Jr. Debate: the slippery slope of surrogate outcomes. *Curr Control Trials Cardiovasc Med* 2000; 1: 76-8.
- Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005; 294: 218-28.
- Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005; 294: 2203-9.
- Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001; 357: 373-80.
- Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; 324: 781-8.
- Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; 360: 196-202.
- Moiseyev VS, Poder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J* 2002; 23: 1422-32.
- Kushwaha SS. Cardiac structure and function. *J Am Coll Cardiol* 2004; 44 (2 Suppl A): 2A-6.
- Cleland JG, Ghosh J, Freemantle N, et al. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-Lipids and cardiac resynchronisation therapy in heart failure. *Eur J Heart Fail* 2004; 6: 501-8.
- Coletta AP, Cleland JG, Freemantle N, Clark AL. Clinical trials update from the European Society of Cardiology Heart Failure meeting: SHAPE, BRING-UP 2 VAS, COLA II, FOSIDIAL, BETACAR, CASINO and meta-analysis of cardiac resynchronisation therapy. *Eur J Heart Fail* 2004; 6: 673-6.
- Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail* 2006; 8: 105-10.
- Teerlink JR, Packer M, Colucci WS, et al. Levosimendan provides rapid and sustained relief in patient global assessment of acutely decompensated heart failure: the REVIVE II study. *J Card Fail* 2006; 12: S86.
- Mebazaa A, Cohen-Solal A, Kleber F, et al. Study design of a mortality trial with intravenous levosimendan — the SURVIVE study — in patients with acutely decompensated heart failure. *J Card Fail* 2004; 10: S81.
- Orlowski JP, Christensen JA. The potentially coercive nature of some clinical research trial acronyms. *Chest* 2002; 121: 2023-8. □