Levosimendan to prevent acute organ dysfunction in sepsis: the LeoPARDS RCT

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Declared competing interests of authors: Anthony Gordon reports personal fees and non-financial support from Orion Corporation Orion Pharma, and grants and other from Tenax Therapeutics during the conduct of the study. He also reports personal fees from Ferring Pharmaceuticals, grants from HCA International, personal fees from GlaxoSmithKline plc, personal fees from Baxter Healthcare Ltd and personal fees from Amomed Pharma outside the submitted work. Daniel McAuley reports personal fees from Peptinnovate Ltd, Bayer, Boehringer Ingelheim Ltd and SOBI, personal fees and other from GlaxoSmithKline plc and grants from the National Institute for Health Research (NIHR), Wellcome Trust and other funders outside the submitted work, as well as a patent being issued for the novel treatment for acute respiratory distress syndrome outside the submitted work. Daniel McAuley is a member of the Health Technology Assessment (HTA) General Board. Mervyn Singer reports grants from the NIHR during the conduct of the study and personal fees from Amomed Pharma outside the submitted work. Anthony Gordon, Gavin Perkins and Daniel McAuley are directors of research for the Intensive Care Foundation.

Published November 2018
DOI: 10.3310/eme05060

Scientific summary

The LeoPARDS RCT

Efficacy and Mechanism Evaluation 2018; Vol. 5: No. 6
DOI: 10.3310/eme05060

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Scientific summary

Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is the most severe form of sepsis and results in circulatory and metabolic abnormalities and is a leading cause of death worldwide. Sepsis is responsible for approximately 30% of all admissions to intensive care in the UK; despite improvements in care, the mortality rate remains high.

Catecholamines are the recommended first-line therapy for septic shock; however, high doses of administered and circulating catecholamines are associated with poor outcomes and severe side effects, including myocardial injury and peripheral ischaemia. A combination of vascular hyporeactivity to catecholamines, myocardial depression and profound vasodilatation can lead to persisting hypotension despite adequate fluid resuscitation.

Levosimendan (Simdax®; Orion Pharma, Newbury, UK) is a calcium-sensitising drug with inotropic and vasodilatory properties licensed for the treatment of acute heart failure. Levosimendan sensitises the myocardium to calcium through binding to troponin C, so that a greater ventricular contraction and stroke volume can be achieved for the same level of intracellular calcium.

When compared with catecholamine use, levosimendan shows an increased myocardial contraction with a minimal increase in oxygen demand, and diastolic relaxation is not affected. Levosimendan also mediates vasodilatation by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle and may have cardioprotective effects.

Several small studies have investigated levosimendan in human septic shock and reported an improvement in haemodynamics, microcirculatory flow and renal and hepatic function. A recent meta-analysis supported its use in sepsis; however, only 125 patients in total were treated.

The LeoPARDS (Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis) trial was designed to determine whether or not levosimendan, when added to standard care, could reduce organ dysfunction in septic shock and to access its safety profile in this group of patients.

Methods

Trial design and participants

The LeoPARDS trial was a multicentre, double-blind, placebo-controlled randomised clinical trial conducted in 34 general adult intensive care units (ICUs) in the UK.

The London – Harrow Research and Ethics Committee approved the trial (reference no. 13/LO/0365). Written consent was obtained from either the patient or, in the event of a lack of capacity, a personal or professional legal representative prior to enrolment into the trial. Retrospective written consent was sought from patients once they regained capacity.

Adult patients (aged ≥ 18 years) who had at least two of four systemic inflammatory response syndrome criteria as a result of known or suspected infection, who had received vasopressors for ≥ 4 hours despite adequate intravenous fluid resuscitation and who were deemed to have an ongoing vasopressor requirement were eligible for inclusion. Patients had to be recruited within 24 hours of meeting the inclusion criteria.

Exclusion criteria were as follows:

- > 24 hours elapsed since meeting all of the inclusion criteria
- end-stage renal failure
- chronic severe hepatic impairment
- history of torsades de pointes
- significant mechanical obstruction affecting ventricular filling and/or outflow
- a treatment limitation decision was in place
- body weight of > 135 kg
- pregnancy
- treated with levosimendan within the previous 30 days
- hypersensitivity to levosimendan or any of its excipients
- enrolled in another interventional trial that might interact with the study drug.

Randomisation and masking

Enrolment, randomisation and data collection were performed via an online system. Patients were assigned to levosimendan or placebo on a 1 : 1 basis with variable block size concealed randomisation using computer-generated random numbers and were stratified by recruitment centre.

Vials of levosimendan and the matching placebo were supplied by Orion Corporation Orion Pharmaceuticals (Espoo, Finland). Trial-specific labelling and packaging, to ensure that trial packs were identical, were undertaken by Victoria Pharmaceuticals (Belfast, UK). Patients and clinical and research staff remained blinded to treatment allocation throughout the trial.

Clinical management

Patients received all normal standards of care and, in addition, were allocated to receive a blinded infusion of either levosimendan or placebo for 24 hours. No bolus loading dose was given. The study drug was commenced at a rate of 0.1 µg/kg/minute and, if tolerated, was increased after 2–4 hours to 0.2 µg/kg/minute for a further 20–22 hours. Patients received intravenous fluid bolus(es) for any clinically significant drop in blood pressure and, if necessary, vasopressors were titrated to maintain an adequate blood pressure. If the 0.2 µg/kg/minute dose was not tolerated, because of either hypotension or severe tachycardia, the infusion rate was reduced to 0.1 µg/kg/minute. If still not tolerated, the rate was reduced to 0.05 µg/kg/minute and, if still not tolerated, the treatment was discontinued.

Other aspects of clinical care were at the local physicians' discretion and based on the Surviving Sepsis Campaign guidelines (Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;**41**:580–637). The study protocol recommended crystalloid infusions as the resuscitation fluid of choice, with noradrenaline as the initial vasopressor, but vasopressin or its analogues could be added to maintain a mean arterial pressure (MAP) of 65–70 mmHg. The MAP target could be varied for individual patients, but investigators were encouraged to use the lowest dose of vasopressor to maintain an acceptable MAP that maintained tissue perfusion in each patient. Hydrocortisone could be added for patients who were poorly responsive to vasopressors (i.e. on high doses of vasopressors). Additional inotropic agents could be used in either treatment group, as clinically indicated, that is, for those with ongoing low cardiac output after fluid resuscitation. Dobutamine was the inotropic agent of choice, with down-titration and discontinuation once an adequate oxygen delivery had been achieved.

Outcome measures

The primary outcome measure of the trial was the mean daily Sequential Organ Failure Assessment (SOFA) score while in the ICU from randomisation to a maximum of 28 days. The daily SOFA score was calculated for each patient based on five organ systems: cardiovascular, respiratory, renal, hepatic and coagulation (maximum score 20). The neurological system was not included because of the difficulties of accurately scoring the Glasgow Coma Scale score daily in the presence of sedation. Daily scores were totalled for

each patient's ICU stay and divided by the number of days they remained in the ICU to calculate the mean SOFA score for each patient.

To assess the effect of levosimendan on individual organ systems, as well as to analyse the individual SOFA components, several clinical outcomes were determined a priori for secondary analyses. These included the number of catecholamine- and ventilator-free days, the time to successful extubation, the proportion of patients with a major acute kidney event over 28 days (defined as death, new requirement for renal replacement therapy or sustained renal failure at day 28) and duration of renal replacement therapy. Mortality rates at 28 days, at ICU and hospital discharge, and at 3 and 6 months, as well as ICU length of stay and serious adverse event rates, were also recorded.

Statistical analysis

A sample size of 500 was chosen to provide 90% power to detect a 0.5-point difference in mean SOFA score assuming a standard deviation (SD) of 1.5 and a significance level of 0.05. To allow for a 3% withdrawal of consent, the recruitment target was 516 patients.

The primary analysis was an unadjusted, intention-to-treat analysis and reported the difference in mean SOFA scores between the two treatment groups. As levosimendan is a known inotrope but is not included as part of the cardiovascular scoring within the SOFA score, a sensitivity analysis was carried out by repeating the primary analysis but excluding the cardiovascular component.

Four subgroup analyses were planned a priori based on baseline measurement of the cardiac index, if measured (lowest tertile vs. middle and highest tertiles); central venous saturations (three groups: low $< 70\%$, normal 70–85%, high $> 85\%$); serum lactate (≤ 2 vs. > 2 mmol/l); and noradrenaline (below vs. above the median infusion rate). The heterogeneity of treatment effect according to subgroup was calculated using a permutation test, permuting both the subgroup and the treatment allocation. All analyses were carried out using R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria), with a p-value of < 0.05 considered statistically significant using two-sided tests.

Results

The trial ran from January 2014 until December 2015, when the required sample size was achieved. Seven patients did not receive the allocated study drug. One patient in the placebo group received open-label levosimendan after receiving the blinded study drug. Two patients in each group died before the study drug could be administered. One levosimendan group patient rapidly improved after randomisation and one placebo group patient was randomised during a temporary halt in recruitment and so was not administered the study drug. These seven patients were included in the analysis. The family of one patient in the levosimendan group withdrew consent after randomisation but before the study drug was administered. This patient was excluded from all analyses.

The two groups were well balanced at baseline and typical of a sick group of septic shock patients, with a median Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 25 (interquartile range 21–30) and a median serum lactate level of 2.3 mmol/l (interquartile range 1.4–3.6 mmol/l). The median time to recruitment was 16 hours after starting vasopressors, and the median dose of noradrenaline was 0.28 µg/kg/minute to achieve a MAP of 74 mmHg (interquartile range 68–79 mmHg) at the time of starting the study drug.

Cardiovascular effects

Thirty-three patients (13.5%) in the levosimendan group stopped the study drug infusion before the 24-hour time point because of haemodynamic instability (hypotension or tachycardia) compared with 19 (7.7%) in the placebo group. The MAP was lower in levosimendan-treated patients in the first 24 hours, but was similar after that time in both groups. The rate and duration of noradrenaline infusion was

higher in the levosimendan group, although there was less frequent use of dobutamine. Heart rate was significantly higher in levosimendan-treated patients over the first 4 days. Intravenous fluid administration, fluid balance and serum lactate levels were similar in both groups.

The primary outcome, the mean SD daily SOFA score over the ICU stay, was 6.7 (SD 4.0) in the levosimendan group and 6.1 (SD 3.9) in the placebo group [mean difference 0.61, 95% confidence interval (CI) –0.07 to 1.29]. After adjusting for ICU, age and APACHE II score in a regression model, the mean difference was 0.59 (95% CI –0.02 to 1.20). When considering each component of the total SOFA score independently, the mean daily cardiovascular score was higher in the levosimendan group than in the placebo group (mean difference 0.25, 95% CI 0.04 to 0.46). As a prespecified analysis, the primary analysis was repeated excluding the cardiovascular component of the SOFA score, giving a mean daily SOFA score of 4.4 SD 3.1 in the levosimendan group and 4.1 (SD 3.1) in the placebo group (mean difference 0.36, 95% CI –0.17 to 0.90).

The mortality rate at 28 days was 34.5% in the levosimendan group and 30.9% in the placebo group (absolute difference 3.6%, 95% CI –4.5% to 11.7%). Patients in the levosimendan group were less likely to be successfully extubated over 28 days than patients in the placebo group (hazard ratio 0.76, 95% CI 0.60 to 0.97). The median number of ventilator-free days was 16 in the levosimendan group and 19 in the placebo group (difference –3.0 days, 95% CI –9.5 to 1.0 days). The number of catecholamine-free days was 22 and 23 in the levosimendan and placebo groups, respectively (difference –1.0 days, 95% CI –4.5 to 1.0 days). In total, 32 levosimendan-treated patients experienced a serious adverse event, compared with 23 patients in the placebo group; supraventricular arrhythmias were more common in the levosimendan group.

No differences in the primary outcome and 28-day mortality rate were seen in any of four predefined subgroup analyses, and there was no significant heterogeneity of treatment effect in any subgroup.

Discussion

In this multicentre, double-blind randomised clinical trial levosimendan did not reduce organ dysfunction when added to standard care for adult patients suffering from septic shock. Patients treated with levosimendan required more noradrenaline, had a higher heart rate and were mechanically ventilated for longer.

Cardiovascular resuscitation is an essential component of sepsis management. However, there is increasing evidence that high doses of catecholamine infusions are associated with worse outcomes. Alternative non-catecholamine vasopressor and inotrope options are thus being investigated. Levosimendan offers an inotropic action through different mechanisms from those of catecholamines. Although levosimendan has a half-life of about 1 hour, its active metabolite, OR-1896, has a long half-life. A single 24-hour infusion should provide haemodynamic effects over a week, long enough to cover the majority of cases of septic shock.

Levosimendan has other important non-inotropic effects. It opens ATP-sensitive potassium channels in vascular smooth muscle, leading to vasodilatation. It may also be protective to the heart and other organs, especially in ischaemia/reperfusion injury. Additional properties include anti-inflammatory, antioxidative and antiapoptotic effects.

In view of these pleiotropic effects and the fact that myocardial dysfunction, although present in > 50% of the septic shock population, may not be clinically evident even when using cardiac output monitoring, we recruited all patients who had septic shock. We also planned four subgroup analyses to examine the effect of levosimendan in higher risk patients, including those with a low cardiac output, those with impaired oxygen delivery to the tissues and those on high doses of catecholamines. There was no evidence of a beneficial effect of levosimendan in any of these prespecified subgroups.

Although levosimendan does not stimulate beta-adrenoreceptors, a significantly higher heart rate was seen in the levosimendan group, most likely as a result of vasodilatation although possibly related to the increased requirement for noradrenaline. Similarly, there was a higher rate of tachyarrhythmias in levosimendan-treated patients, and this may have contributed to the lack of overall clinical benefit.

Patients in the levosimendan group were less likely to be successfully weaned from mechanical ventilation over 28 days. Levosimendan has been reported to sensitise the diaphragmatic muscle to calcium, improve contractility and reverse the development of fatigue after muscle loading. Combined with the prolonged inotropic effect of levosimendan and its active metabolite, levosimendan might have been expected to improve ventilator weaning. It remains unclear why the opposite effect was seen.

There were limitations of the study. This was a trial of levosimendan added to standard care rather than a comparison of levosimendan against an alternative inotrope such as dobutamine. Fewer than 10% of patients in the placebo group received dobutamine. There was no difference in outcome between the groups in the prespecified subgroup analysis of patients with a low cardiac index. In addition, no echocardiographic analyses were performed to provide more detailed information about changes in myocardial function with levosimendan treatment. Therefore, this trial cannot provide guidance as to which inotrope is best to use in the management of sepsis if a very low cardiac index is present.

Conclusions

Among adult patients with septic shock, levosimendan when added to standard care does not reduce organ dysfunction or mortality. Patients allocated to the levosimendan group were less likely to be successfully extubated, had more tachycardia and had a higher rate of supraventricular arrhythmias than those allocated to the placebo group. Therefore, levosimendan cannot be recommended for routine use in septic shock.

Trial registration

This trial is registered as ISRCTN12776039.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. Study drugs were provided by Orion Pharma and additional research funds were provided by Tenax Therapeutics. The study was supported by the NIHR Biomedical Research Centre based at Imperial College, London, and the UK Intensive Care Foundation.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

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Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 11/14/08. The contractual start date was in July 2013. The final report began editorial review in July 2017 and was accepted for publication in June 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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