

## RESEARCH NEWS

# Levosimendan in sepsis: To do or not to do?

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Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis.

Gordon et al. N Engl J Med. 2016;375:1638-48.

**Why was this research done?**

Septic shock results in circulatory and metabolic abnormalities. Persisting hypotension in septic shock is due to vasodilatation, vascular hyporeactivity and myocardial depression. Refractory septic shock is treated with high doses of inotropic support and vasopressors, which can induce high levels of catecholamines. High levels of catecholamines are associated with a poor outcome and side effects such as myocardial injury.

Levosimendan is a calcium-sensitising drug with inotropic and vasodilator properties which increases myocardial contraction. In contrast to catecholamines, these haemodynamic effects of levosimendan are achieved with a minimal increase in myocardial oxygen demand. As calcium levels fall during diastole, relaxation of the myocardium is not impaired with levosimendan, which may be an additional benefit over catecholamines. Besides improving haemodynamic variables, levosimendan has also been shown to have non-inotropic, anti-inflammatory and anti-oxidative effects.<sup>[1-3]</sup> Also, there have been reports regarding possible protection from ischaemia and reperfusion injury by levosimendan.<sup>[4]</sup> A recent meta-analysis supported the use of levosimendan in septic patients; however, only 125 patients were included.<sup>[5]</sup>

**What was the research question?**

In this study, standard care for sepsis (fluids, vasopressors, antibiotics and inotropes) was compared with standard care plus levosimendan. The primary endpoint was the mean daily Sequential Organ Failure Assessment (SOFA) scores assessed at maximally 28 days after randomisation.

**How was this investigated?**

A multicentre randomised controlled, double-blind trial was performed. Patients who met the inclusion criteria (septic shock and use of vasopressors for at least 4 hours) were randomised. The patients were recruited within 24 hours of meeting the inclusion criteria and randomised using an online system.

Patients who were included received either levosimendan or placebo for 24 hours in addition to standard care. There was no bolus loading dose. The intravenous administration rate for both levosimendan and placebo was started at 0.1 µg per kilogram per minute and was increased after 2 to 4 hours to 0.2 µg per kilogram per minute.

The targeted mean arterial pressure was 65-70 mmHg. Hypotension was treated with intravenous fluid boluses and vasopressors. Inotropes were also part of the treatment if indicated.

The primary outcome was the mean SOFA score. The cardiovascular system and neurological system were excluded due to the nature of the study and due to the difficulty in scoring the Glasgow Coma Scale in patients receiving sedatives, respectively.

The secondary outcomes were catecholamine-free, ventilator-free days, the development of acute kidney injury and duration of renal replacement therapy. Mortality, length of stay on the ICU and discharge were also evaluated. The primary analysis was conducted on an intention-to-treat basis.

**Main findings**

A total of 259 patients (51%) were randomised to receive additional levosimendan and 257 (49%) received placebo. The demographic features of both groups were the same, with a mean age 67 years. Patients were predominantly male (56%). The median time to enrolment of the study after meeting the inclusion criteria was 16 hours. The addition of levosimendan

to standard care was not associated with a decrease in organ dysfunction. The mean daily SOFA score did not differ between the two groups: 6.68 (SD 3.96) in the levosimendan group and 6.06 (SD 3.89) in the placebo group ( $p=0.053$ ). There was no difference in catecholamine-free days and the development of acute kidney injury and duration of renal replacement therapy between the two study arms. Patients who were treated with levosimendan required more norepinephrine, had a higher rate of arrhythmia, and had a longer duration of mechanical ventilation than those who received placebo. Mortality at 28 days was 34.5% in the levosimendan group vs. 30.9% in the placebo group ( $p=0.43$ ).

### Consequences for daily practice

This trial does not support adding levosimendan to the standard care of septic shock treatment. However, in this trial a wide range of sepsis patients were recruited without requiring a low cardiac output as an enrolment criterion. A pre-defined subgroup analysis on patients with a low cardiac output also showed no benefit of levosimendan compared with placebo. Unfortunately this subgroup analysis had limited power due to a group size of only 52 patients. Furthermore, this trial does not

answer the question which inotropic agent can best be applied in septic shock as levosimendan was compared with placebo and not to another inotropic agent.

### Disclosures

The author declares no conflict of interest. No funding or financial support was received.

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