

# Prevention of organ dysfunction in septic shock: still looking for an effective treatment

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Severe sepsis and septic shock are currently a major medical issue all over the world. Sepsis has a worldwide estimated incidence of up to 19 million per year (1) and accounts for more than one third of intensive care unit (ICU) admissions (2). Furthermore, reported incidence of sepsis has continuously risen in recent years (3). Despite improvement in patients' care, mortality remains high (2-4), accounting for 5.3 million of deaths every year (5), even if a decrease in mortality rates is evident throughout the last years (3). As a consequence, identifying treatment strategies aimed at improving survival of septic patients is a primary goal of research in the field critical care medicine.

Circulatory alterations are almost invariably present in severe sepsis and septic shock (6). Hypotension is considered a hallmark of these alterations in sepsis (7) and is traditionally attributed to loss of peripheral vascular tone (the so called "distributive shock"). However, myocardial dysfunction has emerged in recent years as a key component of sepsis-induced circulatory dysfunction (8), even in patients with no previous cardiac disease (8). Cardiac output is a key determinant of oxygen delivery to tissues, which ultimately affects end-organ function.

Therefore, treatments targeting cardiac function have been identified as promising strategies to improve outcome of septic patients. Catecholamines such as dobutamine have been traditionally considered first-line agents; unfortunately,

early studies showed a neutral (9) or even a detrimental effect (10) of dobutamine when administered to critically ill patients. This effect has mainly been attributed to the side effects of catecholamines, which include increased myocardial oxygen consumption and arrhythmias (11).

Levosimendan is a relatively new calcium-sensitizer, which has been shown to improve cardiac output with minimal increase in oxygen consumption (12,13). These unique characteristics, together with described anti-inflammatory, anti-oxidative, and anti-apoptotic effects (12,13), make levosimendan a very attractive agent to improve survival in sepsis. In addition, levosimendan may also improve microcirculatory function, another key issue of sepsis-induced organ dysfunction, together with positive effects on kidney, liver, and other organs (14).

Indeed, levosimendan is the most investigated inotrope of the last 20 years (15), and a meta-analysis of randomized controlled trials (RCTs) showed that levosimendan administration might improve survival in patients with severe sepsis and septic shock (16). Furthermore, a network meta-analysis of RCTs ranked levosimendan as the vasoactive drug associated with the highest survival probability in septic patients (17).

Due to these promising pharmacological characteristics and results of early trials, the large, multicenter Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

(LeoPARDS) RCT has been conducted in 34 ICUs of United Kingdom. Results of the LeoPARDS trial have been recently published in the *New England Journal of Medicine* (18). Administration of levosimendan to 516 patients with severe sepsis/septic shock was not associated with improvement in organ function, defined by the Sequential Organ Failure Assessment (SOFA) score. In addition, no difference in 28-day mortality was observed, patients in the levosimendan group were less likely to be weaned from mechanical ventilation as compared with patients in the placebo group and patients allocated to levosimendan presented more supraventricular tachyarrhythmias compared to placebo.

The study has several strengths: it is multicenter, randomized, placebo-controlled, supported by a strong rationale, and has a pragmatic design with minimal changes of everyday clinical practice (19). Due to these characteristics, results of this trial have a strong external validity.

Nevertheless, the trial also has some limitations. Early treatment is a cornerstone of sepsis therapy and previous randomized evidences supported a beneficial effect of levosimendan in septic patients with mortality rate up to 60% (16), thus suggesting that high-risk septic shock patients may receive the greatest benefit from levosimendan infusion if treated early. In their study, Gordon and colleagues enrolled mainly low-risk patients, as reflected by an overall 28-day mortality rate in the control group of 30.9%. Accordingly to this relatively low mortality incidence in the control group, the LeoPARDS was underpowered for mortality, since when supposing a relative risk reduction of 20% or 25%, the sample size should be 2,190 and 1,384 respectively ( $\alpha=5\%$ , power =90%), more than 2-fold the sample size of the study.

In addition, patients were enrolled relatively late after the diagnosis of septic shock (with a median time from shock to randomization of about 15 hours). As previous studies demonstrated, late administration of inotropes to critically ill patients is not associated with an improved outcome (9,10). Finally, patients were enrolled in the study regardless of the presence of a confirmed concomitant cardiac dysfunction (18), therefore, patients might have been exposed to the side effects of levosimendan while not requiring its positive inotropic effect.

This is also related to the dose regimen investigated in the trial. Levosimendan was administered at high dose ( $0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), that is more likely to induce tachycardia and hypotension (13), while previous evidences from meta-analyses suggested the greatest benefit from levosimendan

with doses  $\leq 0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (20). However, it should be noted that a  $0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  infusion was used in the majority of early, single-center trials on levosimendan use in sepsis (16). Despite all these limitations, results of the LeoPARDS trial cannot be ignored. The study provides high-quality evidence that levosimendan administration is ineffective in improving organ function or survival when administered to a general population of septic patients. Levosimendan had relevant side effects in this population: (I) lower mean arterial pressure, mainly in the first 24 hours during infusion of levosimendan, with need of higher doses of norepinephrine than placebo; (II) higher heart rate in the first 4 days than placebo; (III) higher rate of hemodynamic instability necessitating discontinuation of the therapy in 13.5% of the levosimendan patients, as compared to 7.7% in the placebo; (IV) higher incidence of life-threatening supraventricular tachyarrhythmia; and (V) prolonged duration of mechanical ventilation through an unknown mechanism, even if these latter results came from a subgroup analysis.

As a result, we could now add levosimendan to the long list of promising treatments that failed to show to improve septic shock outcome when investigated in multicenter RCTs (21).

Under the clinical and pathophysiological point of view, the subgroup of patients presenting cardiac dysfunction should be the perfect population that could benefit from inotropic therapy. Septic myocardial dysfunction is a well-known but under-diagnosed event that should be systematically evaluated in future trials administering inotropic agents. Inotropic therapy, including mainly dobutamine and levosimendan, remains attractive in these patients, even if randomized evidences are scarce. Further RCTs are warranted to examine the effect of inotropes on clinical outcome of septic patients resending certain degree of myocardial dysfunction, to test if adding an inotrope to these patients is safe and beneficial and to examine which could be the best inotropic agent in these conditions.

Pragmatic multicenter RCTs are currently considered the best available design to investigate the efficacy of treatments (19). Of note, all previous evidences on mortality reduction with levosimendan in septic and perioperative settings were based on small, single-center RCTs of moderate to low quality (16,22): we are waiting for the results of large ongoing perioperative multicenter RCTs (23-25) to see whether levosimendan is only an excellent inotropic drug or also has mortality reduction properties.

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## Footnote

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