Intensive Care Med (2019) 45:1392–1400
https://doi.org/10.1007/s00134-019-05731-w

ORIGINAL

Levosimendan in septic shock in patients with biochemical evidence of cardiac dysfunction: a subgroup analysis of the LeoPARDS randomised trial

David B. Antcliffe[1], Shalini Santhakumaran[2], Robert M. L. Orme[3], Josie K. Ward[1], Farah Al-Beidh[1], Kieran O'Dea[1], Gavin D. Perkins[4,10], Mervyn Singer[5], Daniel F. McAuley[6,7], Alexina J. Mason[8], Mary Cross[2], Deborah Ashby[2] and Anthony C. Gordon[1,9*]

Abstract

Purpose: Myocardial dysfunction is common in sepsis but optimal treatment strategies are unclear. The inodilator, levosimendan was suggested as a possible therapy; however, the levosimendan to prevent acute organ dysfunction in Sepsis (LeoPARDS) trial found it to have no benefit in reducing organ dysfunction in septic shock. In this study we evaluated the effects of levosimendan in patients with and without biochemical cardiac dysfunction and examined its non-inotropic effects.

Methods: Two cardiac biomarkers, troponin I (cTnI) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and five inflammatory mediators were measured in plasma from patients recruited to the LeoPARDS trial at baseline and over the first 6 days. Mean total Sequential Organ Failure Assessment (SOFA) score and 28-day mortality were compared between patients with normal and raised cTnI and NT-proBNP values, and between patients above and below median values.

Results: Levosimendan produced no benefit in SOFA score or 28-day mortality in patients with cardiac dysfunction. There was a statistically significant treatment by subgroup interaction ($p = 0.04$) in patients with NT-proBNP above or below the median value. Those with NT-proBNP values above the median receiving levosimendan had higher SOFA scores than those receiving placebo (mean daily total SOFA score 7.64 (4.41) vs 6.09 (3.88), mean difference 1.55, 95% CI 0.43–2.68). Levosimendan had no effect on the rate of decline of inflammatory biomarkers.

Conclusion: Adding levosimendan to standard care in septic shock was not associated with less severe organ dysfunction nor lower mortality in patients with biochemical evidence of cardiac dysfunction.

Keywords: Septic shock, Levosimendan, Troponin, cTnI, N-terminal prohormone of brain natriuretic peptide, Inflammation

*Correspondence: anthony.gordon@imperial.ac.uk
[9] Intensive Care Unit, Imperial College/St Mary's Hospital, Praed Street, London W2 1NY, UK
Full author information is available at the end of the article

Springer

Introduction

Fluid therapy and catecholamine vasopressors are first-line treatments recommended by the surviving sepsis campaign for the management of septic shock [1]. However, myocardial dysfunction is increasingly recognised in sepsis [2–5] and it is unclear how this should be best treated. Dobutamine is recommended as an inotropic agent [1], but there is concern about the association of beta-adrenergic agonists with an increased risk of myocardial injury and other deleterious effects [6–8].

Recently, the levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial [9] investigated the use of levosimendan in septic shock. Levosimendan is a calcium-sensitising drug which has positively inotropic and vasodilating properties resulting in an increase in cardiac output without increasing myocardial oxygen demand [10]. Levosimendan also has other properties including anti-inflammatory, anti-oxidant and anti-apoptotic effects [11–13] which may also be beneficial in sepsis. The LeoPARDS trial, however, found that the addition of levosimendan to standard treatment in adults with septic shock did not result in less severe organ dysfunction nor lower mortality [9]. However, this trial recruited a wide range of patients with septic shock and it has been suggested that the lack of benefit was because not all patients had cardiac dysfunction [14]. Although the original trial found no benefit of levosimendan in a subgroup of patients with measured low cardiac index, this group was small and prone to missing a clinically important effect. In order to further address the potential differences in effect of levosimendan between those with and without cardiac dysfunction, we performed this pre-specified subgroup analysis of the LeoPARDS trial. We examined the effects of levosimendan in patients with and without biochemical evidence of myocardial injury and dysfunction, as indicated, respectively, by cardiac troponin I (cTnI) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and also its effect on a number of markers of inflammation.

Take-home message

In adult patients with septic shock, adding levosimendan to standard care is not associated with improvement in organ dysfunction nor lower mortality in patients with biochemical evidence of cardiac dysfunction. There is also no evidence to support any potential beneficial immunological effects of levosimendan in sepsis.

Methods

Study design and sample collection

LeoPARDS was a multicentre double-blind, placebo-controlled trial conducted in 34 Intensive Care Units (ICUs) in the United Kingdom between January 2014 and December 2015. Full details of the trial protocol and the primary analysis have been published previously [9, 15]. A full trial report was published by the funder and this manuscript includes a subset of results from this report [16]. The trial was approved by the London–Harrow Research Ethics Committee (13/LO/0365) and written consent was obtained from the patients or their legal representatives.

Adult patients with septic shock who required vasopressors for at least 4 h and were recruited within 24 h of meeting inclusion criteria were eligible for entry into the study. Full details of the inclusion and exclusion criteria can be found in the data supplement. 516 patients were randomised to receive either levosimendan ($n=258$) or placebo ($n=257$) in a 1:1 ratio. Patients and staff were unaware of treatment allocation throughout the trial. One patient in the levosimendan arm withdrew consent and was excluded from further analysis.

Patients received levosimendan or placebo for 24 h in addition to standard care. Drug infusion was started at 0.1 μg/kg/min and increased after 2–4 h to 0.2 μg/kg/min for the remainder of the 24 h. No bolus dose was administered. If patients had rate-limiting side effects, hypotension or severe tachycardia, the rate of infusion could be reduced or the drug stopped. Full details can be found in the data supplement. All other aspects of clinical care were at the discretion of the treating clinicians.

Plasma sample assay methodology

Plasma samples were collected prior to randomisation on the day of inclusion (day 1), after 24 h (day 2) and on days 4 and 6 while still on the ICU. Samples were separated locally (spun at 1000 g for 10 min), frozen according to standardised operating procedures and then sent to the co-ordinating centre in batches for storage and subsequent analysis. All assays were conducted blinded to treatment allocation and outcome.

Two markers of myocardial dysfunction were measured prior to randomisation. CTnI is a widely used marker of myocardial injury and its elevation is associated with cardiac dysfunction and poor outcome in sepsis [17]. Serum NT-proBNP is a biomarker of ventricular dysfunction in septic patients and prognosticates for poor outcomes [18, 19].

CTnI was measured in plasma samples in the clinical laboratories at Imperial College Healthcare NHS Trust using a high-sensitivity chemiluminescent microparticle immunoassay, (Abbott Architect, Abbott Diagnostics, Maidenhead, UK). NT-proBNP was quantified using a sandwich enzyme-linked immunosorbent assay (ELISA)

kit (Abcam, Cambridge, UK), measured in duplicate and with the average of the two values taken.

Five inflammatory biomarkers were also quantified in the collected plasma. The pro-inflammatory cytokine, interleukin 6 (IL-6) and the C–C chemokine ligand 2 (CCL2) have been previously reported to be reduced by levosimendan in sepsis [11]. Soluble tumour necrosis factor receptor 1 (sTNFR1) and the chemokine, interleukin 8 (IL-8) are biomarkers used to characterise a hyper-inflammatory phenotype in critical care that is associated with a higher mortality and a potentially improved response to anti-inflammatory treatment [20]. The anti-inflammatory cytokine, interleukin 10 (IL-10) was also measured. IL-6, IL-8, IL-10 and CCL2 were quantified using the ELLA™ multiplex assay (ProteinSimple, San Jose, CA, USA). Samples were thawed at room temperature, diluted three- to eightfold and run as per the manufacturer's instructions. Positive controls of recombinant IL-6, IL-8, IL-10 and CCL2 standards were run alongside to ensure reproducibility. sTNFR1 was assessed using the ELLA Simple Plex assay (ProteinSimple, San Jose, CA, USA). Samples were thawed at room temperature and were diluted 10- to 13-fold and run as per the manufacturer's instructions alongside positive controls. The ELLA device measures the analytes in triplicate and reports the average value.

Outcomes

The primary outcome was multi-organ dysfunction as measured by the Sequential Organ Failure Assessment (SOFA) score [21]. We only used five components of the score, (cardiovascular, respiratory, renal, liver, and haematological) but, in line with previous sepsis trials [22, 23], not the neurological component due to the confounding effect of concurrent sedative drugs. The final score thus ranged from 0 to 20 for each day. Mean total SOFA score was calculated by taking the average of all SOFA scores for the duration of a patient's intensive care stay. Secondary outcomes were 28-day survival and changes in levels of cardiac and inflammatory biomarkers over the course of intensive care stay.

Statistical analysis

All randomised patients were included in the analysis where possible, unless consent to use the data was withdrawn. For all outcomes, the primary analysis was carried out on an intention-to-treat basis. We pre-specified imputing missing values using the last observation carried forward, as the clinical expectation was that the most likely reason for a measurement not being taken was a lack of change (see Supplementary Appendix for details of the pre-specified statistical analysis plan).

Data are described using median and interquartile range (IQR) for continuous variables, and the number and percentage in each group for categorical variables. The mean total SOFA score is presented as mean and standard deviation (SD). The treatment difference was the unadjusted mean difference in the total mean SOFA score between the levosimendan and placebo arms, with a 95% confidence interval (CI). As the mean SOFA score was not normally distributed, 95% confidence intervals of the mean difference were calculated with the use of bootstrapping, with the application of the percentile method with 100,000 samples.

The mean total SOFA score and 28-day mortality were analysed by pre-specified subgroups of cTnI and NT-proBNP values. The study population was split into two ways:

1. Normal compared with raised values [upper limit of normal values: 34 ng/l for cTnI (Imperial College Healthcare NHS Trust) and 2000 pg/ml for NT-proBNP, according to NICE guidelines [24].
2. Below and above the median value in the study population.

The results of subgroup analysis were displayed using forest plots and permutation tests used to test subgroup differences [25], with a p value below 0.05 denoting statistical significance.

For all biomarkers, Bayesian hierarchical regression models were used to investigate changes in biomarker levels over time, and if trajectories differed between levosimendan and placebo-treated patients. A random intercept term was used to allow for the correlation of multiple measures per patient, with a treatment × time interaction to model differing trajectories in the treatment groups. Adjustment was made for the baseline values of the biomarker (see Supplementary Appendix). As this analysis was exploratory, we investigated models both with and without the treatment × time interaction. Sensitivity analyses were performed adjusting for age and APACHE II score at baseline and allowing for clustering by ICU with a further level of random effects.

To describe the effects of levosimendan, data were presented as: the estimated change in biomarker levels per day for levosimendan and placebo patients; the probability of a faster reduction in biomarker levels in the levosimendan group compared to the placebo group; and the estimated treatment difference on days 2, 4 and 6. All biomarkers, including baseline values, were log transformed to better comply with the assumption of normal error terms, yielding ratios for treatment differences. All analyses were performed with the use of R software,

version 3.2.2 (R Project for Statistical Computing) [26] and WinBUGS version 1.4 [27].

Results

In those patients who had cardiac biomarkers, measured baseline characteristics and demographics were similar between the levosimendan and placebo groups (Table 1).

Cardiac biomarkers

cTnI

CTnI results were available for 442 (86%) patients enrolled into the study (Fig. 1). Patients were divided into groups based on their cTnI results, first into those above or below the upper limit of normal (34 ng/l), and then above and below the median cTnI value (81 ng/l). No interaction was seen between either cTnI group and drug assignment regarding total daily SOFA score (Fig. 2a). However, in those patients with a cTnI raised above normal there was a higher mean SOFA score in those receiving levosimendan than placebo [mean daily total SOFA 6.87 (SD 4.04) vs 5.9 (SD 3.73); mean difference 0.97 (95% CI 0.08–1.86)]. No interaction was seen between either cTnI cut-off method and drug allocation in relation to 28-day mortality (Fig. 2b), although interaction tests have low power in this situation.

Table 1 Baseline characteristics of patients randomised to receive levosimendan and placebo who had samples available for biomarker measurement

Characteristic	Cardiac troponin I measured		NT-proBNP measured	
	Levosimendan ($n=221$)	Placebo ($n=221$)	Levosimendan ($n=202$)	Placebo ($n=217$)
Age (years)	67 (58–76)	68 (58–76)	68 (59–76)	68 (58–76)
Male Sex	124 (56)	124 (56)	112 (55)	119 (55)
Weight (kg)	76 (65–90)	80 (66–94)	75 (65–87)	78 (66–92)
Body-mass index	26 (23–30)	28 (23–32)	26 (23–30)	28 (23–32)
Race, no. white	206 (93)	206 (93)	189 (94)	203 (94)
Recent surgery	78 (35)	82 (37)	73 (36)	78 (36)
Pre-existing conditions				
Ischaemic heart disease	39 (18)	26 (12)	38 (19)	24 (11)
Congestive heart failure	1 (0.5)	2 (1)	1 (0.5)	3 (1)
Cardiac failure	20 (9)	21 (10)	19 (9)	21 (10)
Severe COPD	11 (5)	10 (5)	11 (5)	10 (5)
Chronic renal failure	15 (7)	16 (7)	14 (7)	16 (7)
Cirrhosis	4 (2)	5 (2)	3 (1)	4 (2)
Immunocompromise	20 (9)	22 (10)	20 (10)	21 (10)
Diabetes	57 (26)	44 (20)	52 (26)	45 (21)
Beta-blockers normally taken	46 (21)	38 (17)	44 (22)	34 (16)
Time from shock to randomisation (h)	16 (11–21)	15 (10–20)	16 (11–21)	15 (10–20)
Vasoactive-drug dose at randomisation				
Noradrenaline				
Number	219 (99)	217 (98)	200 (99)	213 (98)
Dose (μg/kg/min)	0.27 (0.15–0.48)	0.26 (0.14–0.43)	0.27 (0.15–0.49)	0.26 (0.14–0.43)
Adrenaline				
Number	14 (6)	15 (7)	13 (6)	13 (6)
Dose (μg/kg/min)	0.11 (0.05–0.21)	0.16 (0.08–0.42)	0.11 (0.06–0.23)	0.16 (0.08–0.45)
Vasopressin				
Number	23 (10)	30 (14)	21 (10)	29 (13)
Dose (units/min)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.03 (0.02–0.04)
Dobutamine				
Number	16 (7)	21 (10)	15 (7)	21 (10)
Dose (μg/kg/min)	6.1 (3.5–9.4)	5.1 (4.4–6.4)	6.4 (3.0–9.5)	5.1 (4.4–6.4)

Continuous variables are given as median and interquartile range and categorical variables as number and percentage

COPD chronic obstructive pulmonary disease

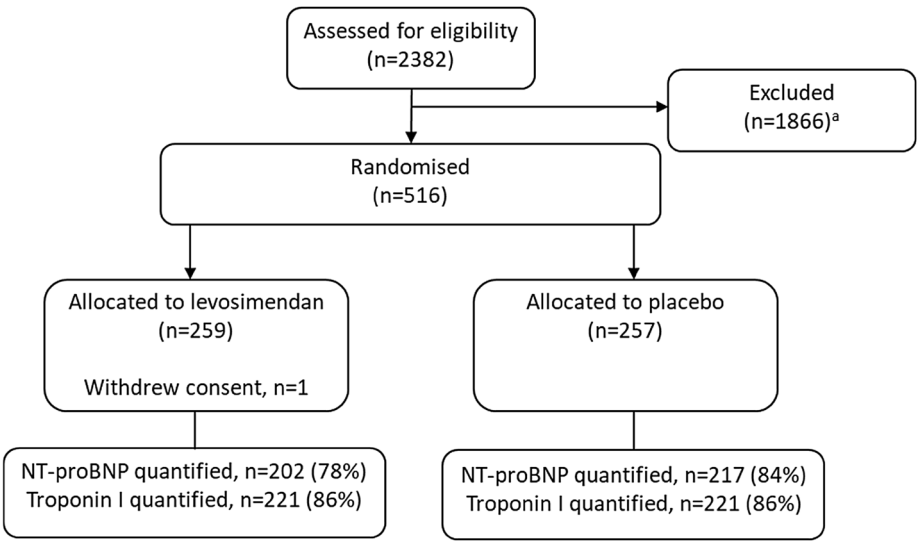

Fig. 1 Recruitment, randomisation and cardiac biomarker measurement of patients recruited to the LeoPARDS study. [a]For a full description of the reasons for exclusion see [9]

CTnI decreased over time in both arms, by 13% per day (95% credible interval [CrI] –26% to 1%) in the levosimendan arm, and by 25% (95% CrI − 35 to − 14%) in the placebo arm (Table 2, Figure S1 of the Supplement), with a probability that cTnI decreased faster in the levosimendan arm of 8%. There was some evidence of a treatment difference only on day 6, but with wide credible intervals (52% difference, 95% CrI 1–219%). A simpler model without the treatment × time interaction along with sensitivity analyses adjusting for age and APACHE II score, and for ICU effects all performed similarly (Table S1 of the Supplement).

NT-proBNP

NT-proBNP measurements were available in 419 (81%) patients (Fig. 1). As with cTnI, NT-proBNP was analysed in two ways. First, by grouping patients with regard to whether their NT-proBNP was above or below the upper limit of normal (2000 pg/ml), and then by splitting based on the median value of 10,268.8 pg/ml. Although no significant interaction was seen between patients with a normal or raised NT-proBNP and treatment allocation ($p = 0.30$) with respect to total daily SOFA score, there was a significant interaction when patients were split based on the median NT-proBNP ($p = 0.04$) (Fig. 2a). Patients with a plasma NT-proBNP level above the median level had a higher SOFA score if randomised to levosimendan [mean daily total SOFA score 7.64 (SD 4.41)], than those receiving placebo [6.09 (SD 3.88)], mean difference 1.55 (95% CI 0.43–2.68). No difference was seen in those with NT-proBNP below the median value (Fig. 2a). Although there was no statistically significant interaction between treatment allocation and NT-proBNP level on 28-day mortality, there was a suggestion that those patients with NT-proBNP values higher than the population median had a higher 28-day mortality if randomised to levosimendan [risk difference 10.50 (95% CI − 2.30 to 23.29)] (Fig. 2b).

NT-proBNP increased on average by 9% (95% CrI 0–19%) per day in the levosimendan group and decreased by 3% (95% CrI – 10 to 5%) in the placebo group (Table 2, Figure S2 in the Supplement). The probability that NT-proBNP decreased faster in the levosimendan arm was 3%. There was some evidence of a treatment difference on day 6 (26% difference, 95% CrI 2–54%) (Table 2). A simpler model without the treatment × time interaction along with sensitivity analyses adjusting for age and APACHE II score, and for ICU effects all performed similarly (Table S2 of the Supplement).

Inflammatory biomarkers

All of the measured inflammatory biomarkers, CCL2, IL-6, IL-8, IL-10 and sTNFr1 decreased similarly over time in both levosimendan and placebo groups (Table 3 and Figure S3 of the Supplementary Material). There was little evidence of a treatment difference on any day for any of the biomarkers. Simpler models without the treatment × time interaction along with sensitivity analyses adjusting for age and APACHE II score, and for ICU effects all performed similarly (Tables S3–S7 of the Supplement).

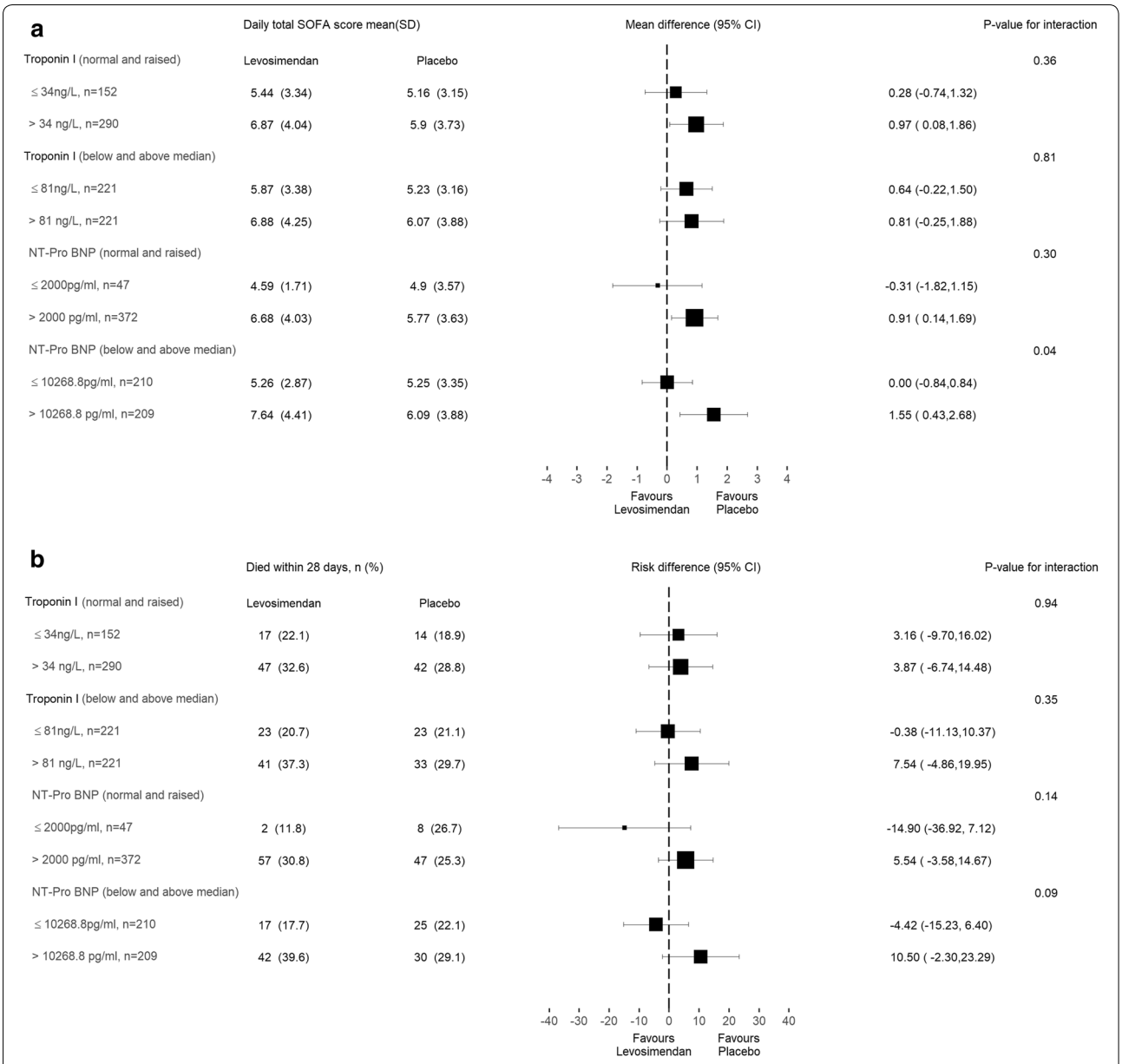

Fig. 2 **a** Forest plot showing the difference in mean total SOFA score, by subgroup based on cardiovascular biomarkers at baseline. **b** Forest plot showing the difference in 28-day mortality, by subgroup based on cardiovascular biomarkers at baseline

Discussion

In this pre-planned sub-group analysis of the LeoPARDS trial we used the biomarkers cTnI and NT-proBNP to identify patients with evidence of myocardial injury and dysfunction, respectively. No benefit from using levosimendan was found in any subgroup classified by a variety of biomarker cut-off thresholds. Indeed, in patients with NT-proBNP levels above the median, higher SOFA scores were seen in the levosimendan group; although not statistically significant, similar trends were seen in patients with elevated cTnI. Using either biomarker, there was a signal to higher 28-day mortality rates in those who had evidence of cardiac dysfunction treated with levosimendan.

Because of its action as a positive inotrope without increasing myocardial oxygen demand, levosimendan has been proposed as a potentially useful treatment in septic shock. LeoPARDs was a double-blind randomised trial comparing levosimendan to placebo in septic shock patients which found no benefit on either rates of organ

Table 2 Estimated effects of levosimendan on cardiovascular biomarkers

Variable	Biomarker	
	Cardiac troponin I	NT-proBNP
Change per day—levosimendan	0.87 (0.74–1.01)	1.09 (1.00–1.19)
Change per day—placebo	0.75 (0.65–0.86)	0.97 (0.90–1.05)
Probability of faster reduction in levosimendan	0.082	0.032
Treatment difference on day 2	1.12 (0.79–1.55)	1.00 (0.84–1.19)
Treatment difference on day 4	1.30 (0.95–1.73)	1.12 (0.96–1.30)
Treatment difference on day 6	1.52 (1.01–2.19)	1.26 (1.02–1.54)

Change per day is expressed as a ratio, treatment differences are given as ratios of levosimendan compared with placebo and data in parentheses are 95% credible intervals

dysfunction nor mortality with the drug [9]. However, because of its properties as an inodilator it has been suggested that levosimendan may only have benefits in those patients with reduced cardiac output or signs of myocardial dysfunction, and the lack of benefit of levosimendan in the original trial may have related to the wide range of patients recruited, with many not having cardiac dysfunction. [14]. Although no specific benefit was seen with levosimendan in those patients with a low cardiac index (≤ 2.44 l/min/m^2) [9], this was a much smaller sub-group than that reported here. The current sub-group analysis adds to the knowledge generated in the original trial by not only demonstrating that patients with biochemical evidence of cardiac dysfunction derive no benefit from levosimendan, but also that in this group there were worse outcomes with levosimendan treatment.

It is not possible from the data available in this study to fully explain why levosimendan does not benefit those patients with evidence of cardiac injury or dysfunction. However, patients randomised to receive levosimendan had higher heart rates, higher rates of supraventricular tachycardia and greater noradrenaline requirements than those receiving placebo [9]. High rates of noradrenaline infusion have been associated with poor outcomes in sepsis [6–8, 28]; it has been proposed that managing tachycardia with beta-blockade may be beneficial in septic shock [29]. It is conceivable that the harm arising from high doses of noradrenaline and tachycardia may be exaggerated in those with pre-existing myocardial damage and dysfunction.

Levosimendan also has reported extra-cardiac effects that may be beneficial in sepsis including immunomodulation with reduction in harmful levels of circulating inflammatory mediators [11, 13]. Five inflammatory biomarkers were measured in the trial population; in all cases similar rates of decline were seen in those randomised to receive levosimendan as those given placebo.

There are a number of limitations to this work. First, it was a sub-group analysis based on samples collected during a multi-centre clinical trial and, as such, samples were not available for all randomised patients (mostly due to lack of research staff out of hours). Cardiac index was only measured in 30% of patients [9], whereas biomarkers were measured in the majority of patients (> 80%) allowing greater power to detect an effect of levosimendan in patients with cardiac dysfunction than in the original analysis. The conclusions drawn in this study are based on biomarker measurement and not on direct assessment of cardiac function with echocardiography. However, both cTnI [17] and BNP [18] have been demonstrated to be robust markers of cardiac injury and dysfunction in sepsis, are easily measured, and are not prone to the same degree of operator dependence as echocardiography. Importantly, all samples were collected, processed and analysed according to standardised procedures and the assays were conducted blinded to treatment allocation and outcome. Longitudinal studies of changes in biomarkers over time are always limited by those patients who either die or are discharged before the end of the study and so do not have samples available for all time

Table 3 Estimated effects of levosimendan on inflammatory biomarkers

Variable	Biomarker				
	CCL2	IL-6	IL-8	IL-10	sTNFr1
Change per day—levosimendan	0.78 (0.73, 0.83)	0.50 (0.44, 0.56)	0.85 (0.80, 0.91)	0.68, (0.63, 0.73)	0.90 (0.86, 0.93)
Change per day—placebo	0.71 (0.66, 0.75)	0.50 (0.45, 0.56)	0.80 (0.75, 0.84)	0.69 (0.65, 0.74)	0.90 (0.86, 0.93)
Probability of faster reduction in levosimendan	0.019	0.536	0.046	0.662	0.500
Treatment difference on day 2	0.89 (0.78, 1.02)	1.00 (0.79, 1.25)	1.00 (0.85, 1.17)	1.06 (0.90, 1.25)	1.02 (0.93, 1.12)
Treatment difference on day 4	0.98 (0.87, 1.10)	0.99 (0.81, 1.20)	1.08 (0.93, 1.24)	1.04 (0.90, 1.19)	1.02 (0.94, 1.11)
Treatment difference on day 6	1.08 (0.92, 1.26)	0.99 (0.74, 1.29)	1.16 (0.97, 1.38)	1.02 (0.85, 1.23)	1.02 (0.92, 1.13)

Change per day is expressed as a ratio, treatment differences are given as ratios of levosimendan compared with placebo and data in parentheses are 95% credible intervals

points. We used a robust pre-specified statistical analysis to account for missing data and to account for truncation of data. No adjustment to reported *p* values was made for multiple comparisons in this study, so the results should be regarded as exploratory.

Conclusion

In adult patients with septic shock, the addition of levosimendan to standard care was not associated with improvement in organ dysfunction nor lower mortality in patients with biochemical evidence of cardiac dysfunction. In fact, patients with NT-proBNP measurements above the median value receiving levosimendan had higher SOFA scores than those receiving placebo. Similarly, there was no evidence to support any potential beneficial immunological effects of levosimendan in sepsis.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05731-w) contains supplementary material, which is available to authorized users.

Author details

[1] Section of Anaesthetics, Pain Medicine and Intensive Care Medicine, Department of Surgery and Cancer, Imperial College London and Imperial College Healthcare NHS Trust, London, UK. [2] Imperial Clinical Trials Unit, Imperial College London, London, UK. [3] Department of Critical Care, Cheltenham General Hospital, Cheltenham, UK. [4] Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Warwick, UK. [5] Bloomsbury Institute of Intensive Care Medicine, University College London, London, UK. [6] Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK. [7] Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, Northern Ireland, UK. [8] Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK. [9] Intensive Care Unit, Imperial College/St Mary's Hospital, Praed Street, London W2 1NY, UK. [10] University Hospitals Birmingham, Birmingham, UK.

Funding

The trial was funded by the Efficacy and Mechanism Evaluation Programme (11-14-08), a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership. Orion Pharma provided levosimendan and placebo free of charge. Tenax Therapeutics provided additional grant support. The NIHR Comprehensive Biomedical Research Centre (based at Imperial College Healthcare NHS Trust and Imperial College London) and the U.K. Intensive Care Foundation provided general research support. ACG is funded by an NIHR Research Professorship award (RP-2015-06-018). The funders, the sponsor (Imperial College London), Orion Pharma and Tenax Therapeutics had no role in designing the trial, gathering or analysing the data, writing the manuscript, nor making the decision to submit the manuscript for publication.

Compliance with ethical standards

Conflicts of interest

The views expressed in this article are those of the authors and not necessarily those of the MRC, the National Health Service (NHS), the NIHR, or the Department of Health. ACG reports receiving speaker fees from Amomed Pharma, consulting fees from Ferring Pharmaceuticals, Baxter Healthcare, Bristol-Myers Squibb and GlaxoSmithKline and grant support from HCA International, all paid to his institution; GDP receives fees for serving on an advisory board for GlaxoSmithKline; DFM receives consulting fees from Peptinnovate, Sobi, Bayer, Boehringer Ingelheim, and GlaxoSmithKline and fees to his institution from GlaxoSmithKline for participating in a clinical trial, and being named on a patent related to a new treatment for the acute respiratory distress syndrome (Canada, US, Australia, and European Union patent no., WO 2011073685, issued to Queen's University Belfast). MS receives consulting fees and grant support from Apollo Therapeutics, Baxter, Deltex Medical, Defence Science and Technology Laboratory, GE Healthcare, Medical Technology Associates II and New Beta Innovation all paid to his institution, and heads a Data Safety Monitoring Board on behalf of Shionogi. No other potential conflict of interest relevant to this article was reported.

Publisher's Note

Received: 24 May 2019 Accepted: 5 August 2019
Published online: 19 August 2019

References

1. Rhodes A, Evans LE, Alhazzani W et al (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377. https://doi.org/10.1007/s00134-017-4683-6
2. Vieillard-Baron A, Caille V, Charron C et al (2008) Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 36:1701–1706. https://doi.org/10.1097/CCM.0b013e318174db05
3. Jardin F, Fourme T, Page B et al (1999) Persistent preload defect in severe sepsis despite fluid loading. Chest 116:1354–1359. https://doi.org/10.1378/chest.116.5.1354
4. Frencken JF, Donker DW, Spitoni C et al (2018) Myocardial injury in patients with sepsis and its association with long-term outcome. Circ Cardiovasc Qual Outcomes 11:1–9. https://doi.org/10.1161/CIRCOUTCOMES.117.004040
5. Aneman A, Vieillard-Baron A (2016) Cardiac dysfunction in sepsis. Intensive Care Med 42:2073–2076. https://doi.org/10.1007/s00134-016-4503-4
6. Schmittinger CA, Torgersen C, Luckner G et al (2012) Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. Intensive Care Med 38:950–958. https://doi.org/10.1007/s00134-012-2531-2
7. Dünser MW, Ruokonen E, Pettilä V et al (2009) Association of arterial blood pressure and vasopressor load with septic shock mortality: a post hoc analysis of a multicenter trial. Crit Care 13:R181. https://doi.org/10.1186/cc8167
8. Andreis DT, Singer M (2016) Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. Intensive Care Med 42:1387–1397. https://doi.org/10.1007/s00134-016-4249-z
9. Gordon AC, Perkins GD, Singer M et al (2016) Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med 375:1638–1648. https://doi.org/10.1056/NEJMoa1609409
10. Ukkonen H, Saraste M, Akkila J et al (1997) Myocardial efficiency during calcium sensitization with levosimendan: a noninvasive study with positron emission tomography and echocardiography in healthy volunteers. Clin Pharmacol Ther 61:596–607. https://doi.org/10.1016/S0009-9236(97)90139-9
11. Wang Q, Yokoo H, Takashina M et al (2015) Anti-inflammatory profile of levosimendan in cecal ligation-induced septic mice and in lipopolysaccharide-stimulated macrophages. Crit Care Med 43:e508–e520. https://doi.org/10.1097/CCM.0000000000001269
12. Hasslacher J, Bijuklic K, Bertocchi C et al (2011) Levosimendan inhibits release of reactive oxygen species in polymorphonuclear leukocytes in vitro and in patients with acute heart failure and septic shock: a prospective observational study. Crit Care 15:R166. https://doi.org/10.1186/cc10307
13. Parissis JT, Adamopoulos S, Antoniades C et al (2004) Effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with decompensated advanced heart failure. Am J Cardiol 93:1309–1312. https://doi.org/10.1016/j.amjcard.2004.01.073
14. Groesdonk H, Sander M, Heringlake M (2017) Levosimendan in sepsis. N Engl J Med 376:798–800. https://doi.org/10.1056/nejmc1616632
15. Orme RML, Perkins GD, McAuley DF et al (2014) An efficacy and mechanism evaluation study of Levosimendan for the Prevention of Acute

oRgan Dysfunction in Sepsis (LeoPARDS): protocol for a randomized controlled trial. Trials 15:199. https://doi.org/10.1186/1745-6215-15-199
16. Gordon AC, Santhakumaran S, Al-Beidh F et al (2018) Levosimendan to prevent acute organ dysfunction in sepsis: the LeoPARDS RCT. Eff Mech Eval 5:1–94. https://doi.org/10.3310/eme05060
17. Landesberg G, Jaffe AS, Gilon D et al (2014) Troponin elevation in severe sepsis and septic shock: the role of left ventricular diastolic dysfunction and right ventricular dilatation. Crit Care Med 42:790–800. https://doi.org/10.1097/CCM.0000000000000107
18. Charpentier J, Luyt C-E, Fulla Y et al (2004) Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 32:660–665. https://doi.org/10.1097/01.ccm.0000114827.93410.d8
19. Post F, Weilemann LS, Messow C-M et al (2008) B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. Crit Care Med 36:3030–3037. https://doi.org/10.1097/CCM.0b013e31818b9153
20. Famous KR, Delucchi K, Ware LB et al (2017) Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med 195:331–338. https://doi.org/10.1164/rccm.201603-0645OC
21. Ferreira FL, Bota DP, Bross A et al (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754–1758
22. Gordon AC, Mason AJ, Perkins GD et al (2014) The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med 42:1325–1333. https://doi.org/10.1097/CCM.0000000000000212
23. Gordon AC, Mason AJ, Thirunavukkarasu N et al (2016) Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA 316:509–518. https://doi.org/10.1001/jama.2016.10485
24. Al-Mohammad A, Mant J, Laramee P et al (2010) Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. BMJ 341:c4130. https://doi.org/10.1136/bmj.c4130
25. Anderson MJ, Ter Braak CJF (2003) Permutation tests for multi-factorial analysis of variance. J Stat Comput Simul 73:85–113. https://doi.org/10.1080/00949650215733
26. R Core Team (2015) R: a language and environment for statistical computing. R Foundation for Statistical Computing
27. Lunn DJ, Thomas A, Best N, Spiegelhalter D (2000) WinBUGS - A Bayesian modelling framework: concepts, structure, and extensibility. Stat Comput 10:325–337. https://doi.org/10.1023/A:1008929526011
28. Boldt J, Menges T, Kuhn D et al (1995) Alterations in circulating vasoactive substances in the critically ill—a comparison between survivors and non-survivors. Intensive Care Med 21:218–225. https://doi.org/10.1007/BF01701475
29. Morelli A, Ertmer C, Westphal M et al (2013) Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock. JAMA 310:1683–1691. https://doi.org/10.1001/jama.2013.278477