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LEVOSIMENDAN IMPROVES HAEMODYNAMIC PROFILE, OXYGENATION INDEX, AND INCREASES THE SUCCESS RATE OF WEANING IN MECHANICALLY VENTILATED ICU PATIENTS WITH IMPAIRED CARDIAC FUNCTION. A CASE SERIES OF 10 PATIENTS

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A b s t r a c t

The authors report on the use of Levosimendan, a calcium sensitiser, a novel inotropic agent in ventilator dependent ICU patients. Ten patients were treated in the intensive care setting with Levosimendan. All 10 patients presented to the ICU with impaired left ventricular function, with catecholamine, and prolonged ventilator dependence. Cardiac performance and ventilatory parameters were evaluated pre and post levosimendan infusion. There was a statistically significant improvement in left ventricular function as evidenced echocardiographically by increase of left ventricular ejection fraction. There was a statistically significant improvement of the oxygenation index (PaO_2/FiO_2 ratio). It was therefore possible to reduce safely FiO_2. Patients who responded to levosimendan with improvement of left ventricular function were more likely to be weaned off mechanical ventilation than non-responders. The authors conclude that Levosimendan appears to provide significant benefit with regard to optimisation of cardiac function and improvement of oxygenation index in ventilator dependent patients with impaired left ventricular function and may potentially facilitate weaning.

K e y w o r d s

Levosimendan, Mechanical ventilation, Weaning, Oxygenation index

A b b r e v i a t i o n s u s e d

FiO_2, inspired fraction of oxygen; LVEF, left ventricular ejection fraction; ICU, intensive care unit; CHF, congestive heart failure; CRRT, continuous renal replacement therapy; PaO_2, arterial partial tension of oxygen; SaO_2, arterial haemoglobin saturation; BP, blood pressure; HR, heart rate; MAP, mean arterial pressure; SD, standard deviation

INTRODUCTION

A novel inotropic agent, levosimendan, is being increasingly used in critically ill patients worldwide, broadening its previously strictly cardiological indications.

There are only very limited data available in the literature regarding use of this calcium sensitiser to optimise cardiac performance in ventilator dependent ICU

patients. On the other hand, there is good evidence of improved long-term prognosis of patients with limited cardiac function treated with levosimendan (1) compared to those treated with conventional inotropes (beta agonists and phosphodiesterase III inhibitors).

Weaning off mechanical ventilation in patients with cardiac dysfunction recovering from critical illness is a complex and sometimes complicated process. Successful weaning requires optimisation of the function of several organs or organ systems amongst which the cardiovascular system plays one of the key roles (2).

This case series report is trying to highlight whether levosimendan could potentially improve some of the parameters of oxygenation and ventilation and eventually could lead to the improvement of the success rate of weaning (3).

MATERIAL AND METHODS

Ten patients admitted to general ICU in a teaching hospital, a tertiary referral centre, between October 2002 and December 2003 were treated with levosimendan. Median APACHE II score was 24.6. Four patients presented after cardiac surgery (3 after coronary artery by-pass grafting, 1 after mitral valve replacement), two following acute myocardial infarction with heart failure, two with acute exacerbation of pre-existing congestive heart failure, two patients with chronic obstructive pulmonary disease and congestive heart failure with combined right and left ventricular failure Prior to initiation of treatment with levosimendan, all ten patients required support with conventional inotropes and vasopressors (dobutamine or combination of dobutamine and noradrenaline) for a median of 6.5 days (5–33 days). Three patients required intra-aortic balloon pump (IABP) support, but at the time of levosimendan administration all patients were already weaned off mechanical circulatory support. The mean dose of dobutamine at the start of levosimendan infusion was 8.7 microgm/kg/min, (5–17.5 microgm/kg/min). Seven out of ten patients were receiving dobutamine in combination with noradrenaline in a mean dose of 0.063 microgm/kg/min (0.01–0.2 microgm/kg/min)

Two patients with acute renal failure were treated with CRRT prior to initiation of levosimendan. There was evidence of only moderate renal impairment at the time of levosimendan initiation in three out of ten patients Levosimendan was given as a 12 mcg/kg loading dose in six patients and then infused in addition to those inotropes and vasopressors already running at a dose of

0.1–0.2 microgm/kg/min for a period of 24 hours. Other four patients received a maintenance dose of 0.1–0.2 microgm/kg/min only (eg without loading dose) as a continuous infusion over 24 hours, because of their haemodynamic instability (noradrenaline dose > 0.1 microgm/kg/min) and/or moderate renal impairment (urea > 13.5 mmol/l, creatinine > 220 micromol/l).

All patients had continuous monitoring of blood pressure (invasively), ECG (lead II and V5), and SaO2 during and after the infusion of levosimendan. Only 2 patients post cardiac surgery had invasive haemodynamic monitoring via a Swan-Ganz floating catheter. Twelve-lead ECG was taken three times during levosimendan infusion and the potassium level was checked 4 hourly. LVEF was measured echocardiographically by two certified operators 12–24 hours prior to commencement and 12–24 hours after termination of levosimendan infusion.

The statistical method used to compare changes of measured physiological parameters was a paired T-test calculated with GraphPad QuickCalcs software

RESULTS

There was an improvement in left ventricular function as evidenced echocardiographically by a statistically significant ($p = 0.02$) increase from pre-infusion (29.5 %)

to post-infusion (36.5 %) left ventricular ejection fraction. Following the use of levosimendan there was also a highly statistically significant

(p = 0.003) increase of the oxygenation index (172 pre-infusion to 190 post-infusion)

Improvement of OI allowed a statistically significant (p = 0.0005) reduction in FiO_2 from 0.475 to 0.405. Other monitored parameters (eg SaO_2, BP mean, BP systolic, BP diastolic and heart rate) showed no significant difference pre and post levosimendan infusion.

Selected measured parameters are summarised in the following table:

	Pre infusion (SD)	Post infusion (SD)	p value
Heart rate (b/min)	90 (11)	89 (12)	0.6
MAP (mmHg)	84 (12.3)	87.2 (11.9)	0.51
SaO2 (%)	95.8 (2.1)	96.1 (1.8)	0.9
OI (PaO2/FiO2)	172 (5.62)	189 (13.6)	0.003
FiO2	0.475 (0.09)	0.405 (0.09)	0.0005
LVEF (%)	29.5 (4.97)	36.5 (7.1)	0.02

Conventional inotropes (dobutamine) were weaned in all cases within 24 hours and vasopressors (noradrenaline) were weaned in all cases during the following 1–5 days after completion of levosimendan infusion without any signs of haemodynamic instability. In three cases it was necessary to increase the dose of noradrenaline due to transient hypotension during administration of the loading dose. No other adverse effects (myocardial ischemia, prolonged QT, hypokalemia or dysrhythmias) were noted.

Six out of ten patients were successfully weaned off mechanical ventilation and survived to discharge from hospital. Two patients were extubated within 12 hours after termination of levosimendan infusion. The average time from termination of levosimendan infusion to successful weaning (defined as 48 hours without need of any ventilatory support) was 3.6 days (2–4). A subgroup of six patients with previous long-term ventilator dependence, eg > 2 weeks, all of them tracheotomised, showed an interesting difference with regard to weaning off ventilatory support. Those who responded to levosimendan and showed increase in LVEF > 5 % were subsequently successfully weaned (2 patients). Four patients without any improvement or with an increase of LVEF just equal to 5% were impossible to wean and all of them died. Of the four who died (day 9–32 post levosimendan infusion), two died from sepsis, one from multiorgan failure, and one from successive myocardial infarction.

DISCUSSION

Drugs routinely used in many ICU's to optimise cardiac function – such as catecholamines and phosphodiesterase III inhibitors – have been shown to have major setbacks with regard to short-term effects, eg tachyphylaxis (*4*), and especially to long-term prognosis (*5,6*). Levosimendan acts through direct binding with troponin-C, thereby increasing the affinity of troponin-C for calcium in calcium dependent manner causing enhanced actin-myosin cross-bridging, and hence increased strength of systole (*7*) without additional energy and oxygen requirements.

During diastole (under low prevailing calcium concentrations) levosimendan, unlike other calcium sensitisers, does not show any "calcium sensitising effect"(*7*).

This is probably of great importance for the prevention of potential worsening of diastolic dysfunction (*8*). In addition, the long-lasting pharmacodynamic effects of levosimendan metabolite OR-1896 (5–9 days) may help to maintain improved cardiac performance (*9*) during prolonged weaning and even during the first 24–48 hours after extubation, which is often a very problematic phase.

Via opening ATP-dependent K channels levosimendan causes clinically significant vasodilatation predominantly within coronary and pulmonary vasculature (*10*) and improves O_2 supply to myocardium and reduces right ventricular afterload. An increasing number of patients with congestive heart failure receiving chronic beta blockade (*11*) present to ICU's worldwide with acute decompensation. Administration of beta-agonistic drugs such as dobutamine is often ineffective or could be even harmful because of a competing mechanism of action and the need for much higher doses of beta agonists to obtain the desired haemodynamic effect (*12*). This may be another rationale why levosimendan could be a good therapeutic option for ventilator dependent patients with failing myocardium. Positive haemodynamic effects have been demonstrated by *Nijhawan* also in a group of patients undergoing cardiac surgery with the use of cardiopulmonary by-pass (*13*).

The reported case series shows that levosimendan can be used in critically ill patients with prolonged ventilator dependency and those with significant increase of their LVEF are more likely to be successfully weaned off ventilator support compared to those who do not respond to levosimendan administration. The improved success rate of weaning may be directly attributed to the improvement in cardiac performance, since there was no difference between pre and post infusion results of other important parameters such as renal function (urea, creatinine), levels of potassium, phosphates, calcium, magnesium, thyroid function tests, level of consciousness, and muscle power.

Nutritional parameters were not measured but it is unlikely to expect any significant changes within 24–48 hours of levosimendan infusion. To validate the observed results as well as the prognostic value of responsiveness to levosimendan with regard to the subsequent weaning success (non-responders did not survive), we will need much larger studies to be conducted in the future.

CONCLUSION

We conclude that Levosimendan appears to be safe and may offer a significant benefit with regard to improvement of oxygenation in ventilator dependent patients with impaired cardiac function. Despite the limited number of patients reported in this case series the authors believe that levosimendan may potentially facilitate the weaning process and can improve the success rate of weaning off mechanical ventilation in patients with limited cardiac function.

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LEVOSIMENDAN ZLEPŠUJE HEMODYNAMICKÝ PROFIL, OXYGENAČNÍ INDEX A ÚSPĚŠNOST ODPOJOVÁNÍ VENTILOVANÝCH PACIENTŮ INTENZIVNÍ PÉČE SE ZHORŠENOU SRDEČNÍ FUNKCÍ. KAZUISTIKY 10 PACIENTŮ

S o u h r n

Autoři referují zkušenosti s použitím levosimendanu, nového inotropika u pacientů intenzivní péče, závislých na umělé plicní ventilaci. Deset pacientů bylo léčeno levosimendanem v podmínkách oddělení intenzivní péče. Všech 10 pacientů bylo přijato se známkami zhoršené funkce levé komory, závislostí na katecholaminech a bylo dlouhodobě na umělé plicní ventilaci. Srdeční výkonnost a ventilační parametry byly měřeny před a po podání infúze levosimendanu. Bylo zaznamenáno statisticky významné zlepšení funkce levé komory, což bylo prokázáno echokardiograficky jako zvýšení ejekční frakce levé komory. Došlo ke statisticky významnému zvýšení oxygenačního indexu (poměru PaO2/FiO2), bylo tedy možno bezpečně snížit inspirační frakci kyslíku (FiO2). Pacienti, u nichž došlo ke zlepšení funkce levé komory po podání levosimendanu, měli vyšší pravděpodobnost úspěšného odpojení od umělé plicní ventilace než pacienti, kteří na levosimendan nezareagovali.

Autoři uzavírají, že podání levosimendanu může poskytovat významnou výhodu při optimalizaci srdeční funkce a zlepšení oxygenačního indexu u pacientů závislých na umělé plicní ventilaci se srdečním selháváním a případně usnadnit jejich odpojování od umělé plicní ventilace.

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