Original Article

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The use of levosimendan in shocked patients with compromised left ventricular function and requiring catecholamine support – A case series

Anthony S. McLean, Marek Nalos, Stephen J. Huang, Iris Ting

Abstract

***Objective*: Levosimendan is a calcium sensitizer that improves cardiac contractility without increasing intracellular calcium level, hence energy demand. Theoretically, it is safer to use levosimendan than catecholamine in shocked patients who require inotrope support. Studies on the use of levosimendan in shocked patients are, however, limited. In this case series, we describe the pre- and post-infusion effects of levosimendan in shocked patients with reduced cardiac function and requiring catecholamine inotrope support.**

***Design*: A case-series report.**

***Setting*: The intensive care unit of a teaching hospital.**

***Patients*: Fifteen shocked patients with reduced left ventricular ejection fraction and requiring catecholamine inotrope support were reviewed retrospectively.**

***Intervention*: 24 hour intravenous infusion of levosimendan with concomitant noradrenaline infusion.**

***Results*: In response to 24-h levosimendan infusion, the left ventricular ejection fraction increased from 25.7 ± 11.0% to 29.8 ± 8.6% (P = 0.0389), and the plasma B-type natriuretic peptide reduced from 993 ± 389 to 644 ± 408 pg/ml (P = 0.0015). The blood lactate also demonstrated a significant decrease. During infusion, the mean arterial blood pressure (MAP) was maintained above 65 mmHg by concomitant noradrenaline infusion. The noradrenaline dosages required to maintain the MAP were reduced at the end of infusion. No adverse event related to the drug was seen during the infusion.**

***Conclusion*: Levosimendan leads to an improvement in the hemodynamic status of the shocked patients with compromised left ventricular function. This improvement was reflected by an improvement in LVEF, the favorable changes in BNP and blood lactate levels. Levosimendan is safe to use and may present an alternative to catecholamine inotropes in the management of shocked patients with reduced cardiac function and requiring inotrope support.**

Keywords: Levosimendan; shock; sepsis; acute heart failure; B-type natriuretic peptide; case series

Introduction

Shock is characterized by hypotension and/or hypoperfusion, where oxygen delivery to vital organs is compromised [1,2]. It may be accompanied by inadequate cardiac performance [3]. Following fluid resuscitation, inotropes and vasoactive agents are sometimes used to manage circulatory failure [4]. Catecholamines, such as dobutamine, are the most commonly used inotropes for enhancing the cardiac contractility. They increase the availability of intracellular calcium, and have the drawbacks of increasing myocardial energy burden and arrhythmias [5]. Other adverse effects of catecholamine inotropes may include the aggravation of flow maldistribution and the long-term mortality in heart failure [6-8].

Levosimendan is a calcium sensitizer used intravenously for the management of heart failure [9]. At thera-

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peutic dose, levosimendan acts predominantly as calcium sensitizer (inotrope) and ATP-sensitive K^+-channel (K_{ATP}-channel) opener [10]. It binds directly to the calcium-dependent site on troponin C, stabilizing the calcium-induced conformational change and enhances the calcium sensitivity of the cardiac myofilaments [11]. The main advantages of calcium sensitizer over dobutamine are the lack of intracellular calcium overload and little increase in the energy demand for handling intracellular calcium. In theory, this results in a lower incidence of arrhythmias [12]. Levosimendan also causes regional vasodilation via its K^+-channel opening activity, resulting in the increase coronary blood flow and organ perfusion [13,14].

In the last 12 months, levosimendan was administered in fifteen severe shocked patients in our Intensive Care Unit in order to improve their cardiac contractility, and hence hemodynamic status. The purpose of this case series report was to summarize our experience in using levosimendan in shocked patients with reduced cardiac function requiring catecholamine treatment. We presented the pre- and post-infusion changes in the left ventricular ejection fractions (LVEF), plasma B-type natriuretic peptide (BNP) concentrations, and other hemodynamic indices.

Methods

Prescription of levosimendan

Levosimendan was prescribed to fifteen shocked patients with reduced LVEF and requiring catecholamine inotrope for maintaining hemodynamic stability. All patients displayed (a) reduced left ventricular systolic functions with LVEF < 45% or with cardiac index < 2.5 L/min/m^2; (b) reduced mean arterial pressure (MAP < 65 mmHg) or required noradrenaline to maintain a MAP of over 65 mmHg; and (c) signs of hypoperfusion as demonstrated by reduced urine output (< 0.5 ml/kg/hr) or hyperlactatemia (blood lactate > 2 mmol/L). Written informed consents were obtained from the patients or their relatives for using levosimendan. Authorisations to use the drug were obtained from the Australian Therapeutic Goods Administration.

Levosimendan was infused intravenously with a loading dose of 12 μg/kg over 10 minutes followed by continuously infusion at a dose of 0.1 μg/kg/min for 24 hours. The arterial blood pressure was monitored via arterial catheters. Intravenous noradrenaline was administered, when necessary, to maintain the MAP > 65 mmHg.

Echocardiographic LVEF and plasma BNP were measured before and after (within 1 hour) levosimendan infusion. Plasma BNP concentrations were measured using the Triage BNP meter (Biosite Diagnostics Inc; San Diego, California) [15]. Other blood tests were carried out routinely as part of standard management and care.

Statistics

Unless otherwise stated, the results were expressed as mean ± SD [median]. The non-parametric Wilcoxon signed-rank test was employed for paired comparisons. Correlation studies were made using Spearman Rank correlation test. Friedman ANOVA was used in repeated measures study. The Kendall coefficient of concordance was also provided to express the degree of association between the correlated samples. A 5% confidence level was regarded as significant. The upper detection limit for the Triage BNP meter was 1300 pg/ml. BNP concentrations over 1300 pg/ml were taken as 1300 pg/ml in the analyses.

Results

Patients

A total of three females and twelve males, aged 20 to 80 (mean: 60.9 ± 16.4), were treated with levosimendan. The Apache II score was 21.3 ± 6.4 which was significantly higher than the average Apache II score for our general intensive care unit (ICU) population (15.0 ± 8.6, $P = 0.013$). The average length of stay (LOS) in ICU was 12.3 ± 9.1 [9.3] days, which was significantly longer than the general ICU population (4.7 ± 6.6 [2.4] days; $P < 0.001$).

The baseline LVEF was reduced in these patients (25.7 ± 11.0%). The BNP concentration was elevated when compared to a cutoff value of 140 pg/ml for intensive care patients without cardiac abnormalities (mean: 993 ± 389 [1150] pg/ml) ($P < 0.001$) [15]. The baseline serum concentrations of lactate, creatinine and bilirubin are shown in **Table 1**.

Effects of levosimendan

The heart rate and MAP remained stable during the course of levosimendan infusion, (**Figure 1**). The hourly dose of noradrenaline required to maintain the MAP peaked at the second hour and then showed a gradual and significant fall over the remainder of the course (Friedman ANOVA $P = 0.013$; Kendall concordance = 0.19) (**Figure 1**).

The LVEF showed a significantly but relatively small improvement in response to levosimendan infusion (Pre:

TABLE 1. SUMMARY OF PATIENT CHARACTERISTICS*

Number of patients	15
Male : Female	12 : 3
Mean age	60.9 ± 16.4 63]
Mean Apache II score	21.3 ± 6.4 [20]
Average LOS (days)	10.6 ± 6.6 [9]
% Deceased	46.7%
Mean LVEF	25.7 ± 11.0% [23%]
Mean plasma BNP (pg/ml)	993 ± 389 [1150]
Mean blood lactate (μmol/L)	4.17 ± 4.04 [2.46]
Mean serum creatinine (μmol/L)	180 ± 72 [152]
Mean serum total bilirubin (μmol/L)	17.7 ± 21.4 [11]
Mean serum aspartate aminotransferase (U/L)	1094 ± 2037 [123]

*VALUES GIVEN AS MEAN ± SD [MEDIAN] UNLESS OTHERWISE INDICATED

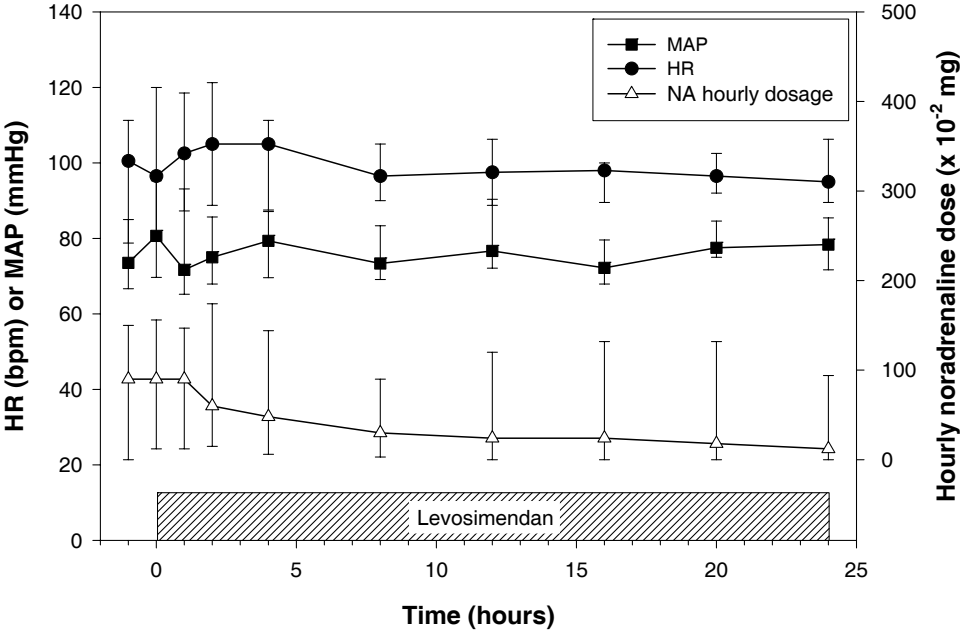

FIGURE 1. TIME COURSE SHOWING THE CHANGE IN HEART RATE (HR), MEAN ARTERIAL BLOOD PRESSURE (MAP) AND HOURLY NORADRENALINE (NA) DOSAGE DURING THE 24H LEVOSIMENDAN INFUSION. RESULTS WERE PRESENTED AS MEDIAN (75TH PERCENTILE). THE CHANGES IN THE NORADRENALINE DOSAGE WERE SIGNIFICANT (FRIEDMAN REPEATED MEASURE ANOVA $P = 0.013$; KENDALL CONCORDANCE = 0.19).

25.7 ± 11.0% *vs* Post: 29.8 ± 8.6%; $P = 0.039$) (**Figure 2**). The plasma BNP concentrations demonstrated a significant decrease, from 993 ± 389 to 644 ± 408 pg/ml, before and after levosimendan infusion ($P = 0.001$) (**Figure 3**). However, there was no correlation between the changes in LVEF and BNP ($r^2 = 0.074$; $P = 0.326$) nor was there any correlation between the baseline LVEF and BNP values ($r^2 = 0.002$; $P = 0.87$).

The blood lactate was decreased by 0.99 ± 2.47 mmol/L (from 4.50 ± 4.26 [2.52] to 3.51 ± 5.53 [1.78] mmol/L; $P = 0.0119$). There was no significant change in serum creatinine and serum aspartate aminotransferase levels. The mean baseline SOFA score was 8.2 ± 2.5. The score was reduced to 5.2 ± 3.9 the day following the infusion and was further decreased to 3.9 ± 3.4 at day 7 (Friedman ANOVA $P < 0.001$; Kendall concordance = 0.72). A

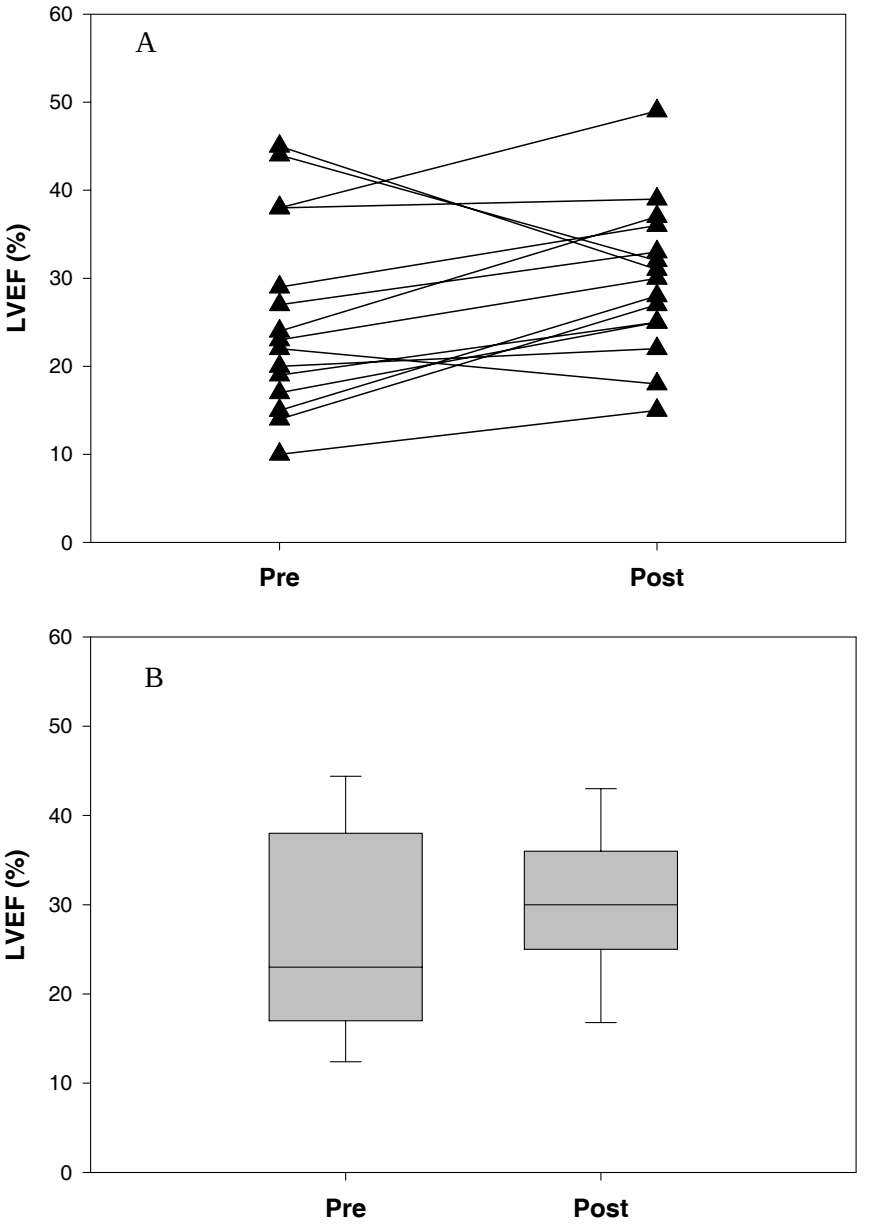

FIGURE 2. THE CHANGE IN LVEF BEFORE (PRE) AND AFTER (POST) 24H LEVOSIMENDAN INFUSION. A, CHANGE IN LVEF FOR INDIVIDUAL PATIENT. B, BOX PLOTS SHOWING THE CHANGE IN THE MEDIAN VALUES: BAR: 5TH/95TH PERCENTILES.

similar significant downward trend was also observed for the cardiovascular component of the SOFA score (Friedman ANOVA $P < 0.001$; Kendall concordance = 0.69) (**Figure 4**).

Adverse effects of levosimendan

The MAP was satisfactorily controlled during the infusion by concomitant noradrenaline administration in these patients (**Figure 1**). Two patients, who had episodes of ventricular fibrillation (VF) prior to levosimendan infusion, experienced VF episodes during the infusion. Otherwise, no serious adverse event was presented during the infusion.

A total of four patients died during their stay in ICU, and three died in the hospital after being discharged from ICU. The main causes of death were VF arrests (two patients) or multiorgan failures (four

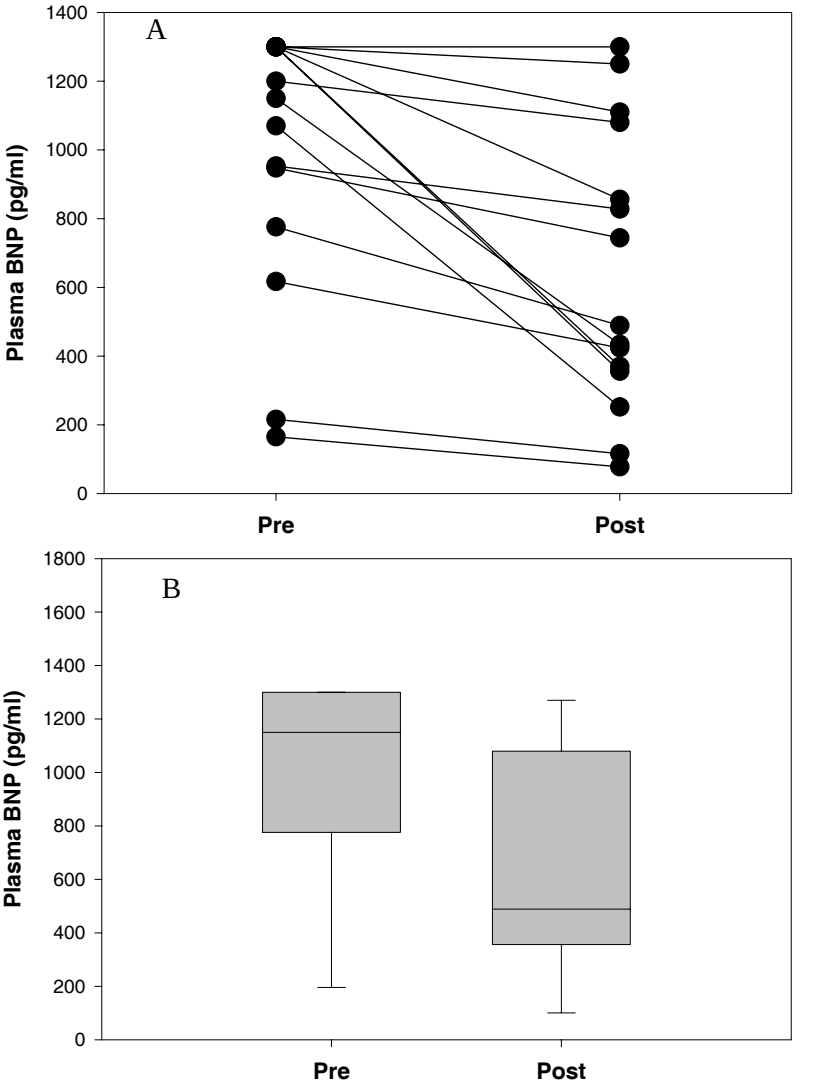

FIGURE 3. THE CHANGE IN PLASMA BNP CONCENTRATIONS BEFORE (PRE) AND AFTER (POST) 24H LEVOSIMENDAN INFUSION. A, CHANGE IN BNP FOR INDIVIDUAL PATIENT. B, BOX PLOTS SHOWING THE CHANGE IN THE MEDIAN VALUES: BAR: 5TH/95TH PERCENTILES.

patients). One patient died of heparin-induced thrombocytopenia.

Discussion

The main findings of this case series study are that levosimendan is feasible in treating shocked patients who require catecholamine inotrope support. There were no change in heart rate and MAP during the course of infusion. The patients became less reliant on noradrenaline to maintain MAP at the end of infusion. Although this may be interpreted as the natural course of shock and no control group is presented, levosimendan was prescribed, especially in the first few cases, as a last resort therapy without which the likelihood of shock reversal was minimal. Levosimendan significantly reduced the BNP and lactate concentrations upon infusion. Improvement in organ functions was documented by the reduced total SOFA score. Although the use of noradrenaline has made the interpretation of LVEF difficult, it is safe to assume that levosimendan improved the LVEF, at least mildly, because the noradrenaline requirement (as would its effect on cardiac contractility) was reduced at the end of infusion.

One of the concerns in using levosimendan in

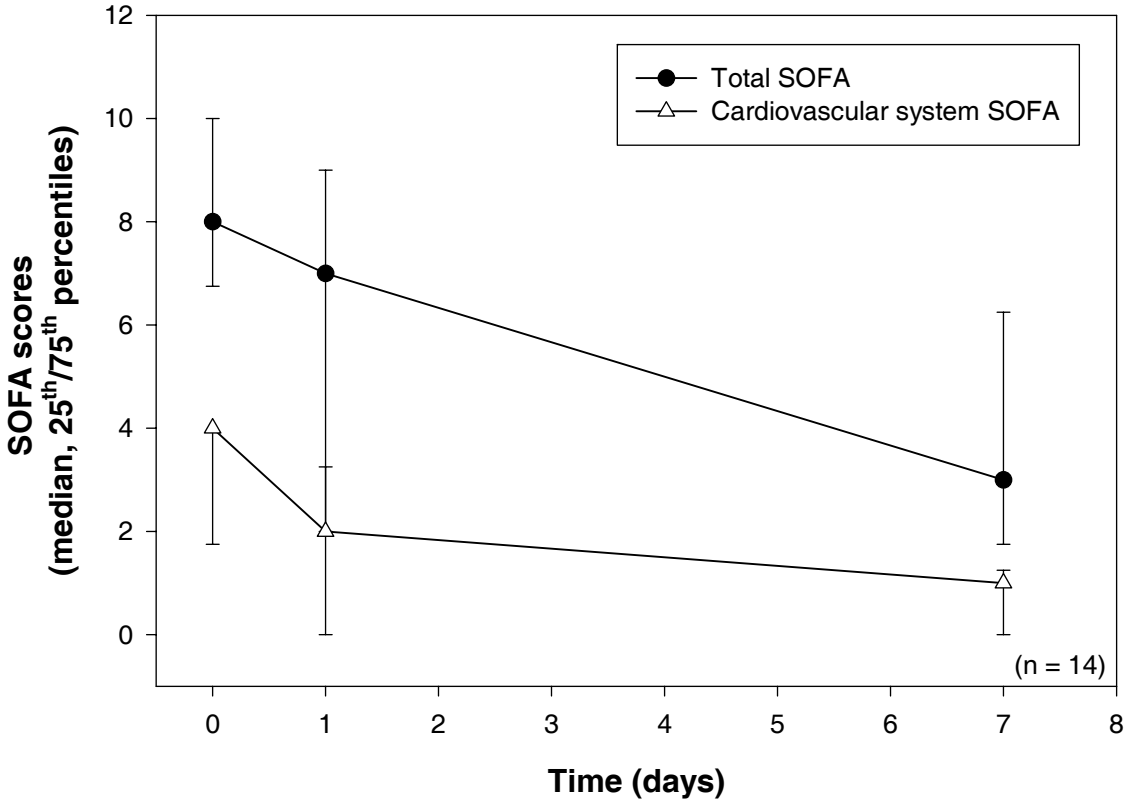

FIGURE 4. THE CHANGE IN SOFA SCORE SINCE LEVOSIMENDAN INFUSION. RESULTS WERE EXPRESSED IN MEDIAN (BAR: 25TH/75TH PERCENTILES). ONE PATIENT WAS EXCLUDED BECAUSE SHE DIED FEW HOURS AFTER THE INFUSION STOPPED.

shocked patients is its vasodilatory effects in these hemodynamically unstable patients. It is envisaged that levosimendan may worsen their conditions by furthering lowering the blood pressure [16]. However, this study demonstrated that the hypotensive effect of levosimendan was minimal and could be effectively controlled by the concomitant use of noradrenaline.

Plasma BNP concentrations are elevated in a wide variety of heart conditions, and is released mainly by the cardiac ventricles in response to volume or pressure overload (increased preload or afterload) [17,18]. It is also raised in septic shock patients with sepsis-induced myocardial depression [19,20]. In the present study, all patients presented with compromised left ventricular systolic function. They either had underlying cardiac aetiologies or developed sepsis-induced myocardial depression or both. The baseline plasma BNP levels were increased in all patients, consistent with the reduced baseline LVEF. The improvement (reduction) in plasma BNP in response to levosimendan suggested an improvement in cardiac functions or loading conditions. This notion was supported by the small but yet significant increase in LVEF. These results were consistent with other findings. For example, it has been shown recently that levosimendan resulted in a reduction in pulmonary capillary wedge pressure (PCWP) in cardiogenic shock patients, and a fall in PCWP was associated with a fall in plasma BNP levels [21,22]. In an experimental porcine model of endotoxemia, levosimendan attenuated endotoxin-induced pulmonary hypertension, improved cardiac output and reduced systemic vascular resistance [23]. A recent study also demonstrated that levosimendan attenuated endotoxin-evoked myocardial dysfunction in isolated heart preparation [24].

Hyperlactatemia is commonly seen in all form of shock and is associated with low flow or tissue hypoxia [25]. Elevated blood lactate can result from increased production and reduced clearance, both of which can be the direct results of tissue perfusion [26-28]. In the present study, the observed reduction in blood lactate following levosimendan treatment suggests improved perfusion and/or oxygen delivery status in these patients. The improvement in the total SOFA scores provided support for such a notion [29].

Limitation

As this is a retrospective case series, we were unable to control the conditions of the study. For example, we were unable to report the changes in PCWP, systemic vascular resistance and cardiac index because of the lack of indwelling catheters in some of these patients. Due to the ready availability of echocardiography, the justification of using extra invasive procedures or monitoring is becoming difficult.

Although the hemodynamic parameters might be interfered by the concomitant use of analgosedation, the effects would be minimal because these patients received constant analgosedation at least 6 hours prior and throughout the infusion period.

Conclusion

This series demonstrated that the use of levosimendan in shocked patients was feasible and, perhaps, holds promise as an alternative to catecholamine inotropes. An overall improvement in the hemodynamic status of the patients was suggested by the decreasing dose of noradrenaline, improving BNP and lactate levels as well as the SOFA scores. The main reported side effect is vasodilatation that can possibly aggravate hypotension. In this regard, we showed that the blood pressure could be effectively controlled by the concomitant administrations of noradrenaline. Whether or not levosimendan can replace catecholamine in this group of shocked patients would require prospective clinical trials.

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