Effect of Levosimendan in Patients with Severe Systolic Heart Failure and Worsening Renal Function

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Abstract

Background: Levosimendan, a calcium sensitizer, increases the sensitivity of the heart to calcium, thus increasing myocardial contractility without a rise in intracellular calcium. It was recently shown that levosimendan is beneficial in improving renal function. However, it remains to be established that the beneficial effect is differentially related to renal status during index event.

Objective: The purpose of the current study was to determine whether levosimendan could improve renal outcome in acute decompensated heart failure patients with and without worsening renal function.

Methods: Forty-five consecutive patients who had a reduced glomerular filtration rate and had at least two consecutive data regarding renal function prior to administration of levosimendan were enrolled in the study. Patients were classified into two groups as those with and without worsening renal function based on an increase in serum creatinine >0.3 mg/dL.

Results: A significant improvement was noted in renal function in patients with worsening renal function (serum creatinine from 1.4±0.16 to 1.21±0.23 mg/dL, p=0.001 and glomerular filtration rate level from 48.9±15 to 59.3± 21.8 mL/min/m², p=0.011), while there was no significant improvement in those without worsening renal function (serum creatinine from 1.29±0.33 to 1.37±0.66 mg/dL, p=0.240 and glomerular filtration rate level from 53.7±17.6 to 52.9±21.4 mL/min/m², p=0.850).

Conclusion: Levosimendan appears to provide a renal-enhancing effect in patients with severe, acute decompensated systolic heart failure and worsening renal function. Consideration of this differential effect might help obtain beneficial renal outcomes. (Arq Bras Cardiol 2012;98(6):537-543)

Keywords: Heart failure; levosimendan; worsening renal function; renal-enhancing effect; creatinine; glomerular filtration rate

Introduction

Worsening renal function is a well-established predictor of adverse outcomes and prolonged length of hospital stay in patients with heart failure (HF)[1,2]. Renal dysfunction is highly prevalent among patients with chronic HF. In fact, renal dysfunction has been reported to occur in one of four patients with HF[2]. The risk for morbidity and all-cause mortality in patients with HF gradually increases with an increase in creatinine or a decrease in the glomerular filtration rate[1]. Thus, in order to define the complex interaction between the heart and kidneys, the term "cardiorenal syndrome" was introduced[3]. Due to the complex nature of interaction between the heart and kidneys, cardiorenal syndrome has been divided into five different subtypes[3]. A deteriorated heart function may impair the function of the kidney both acutely and chronically, or vice versa. In the first subcategory of cardiorenal syndrome, abrupt deterioration of cardiac function brings about acute kidney injury, whereas, in the second subcategory, chronic cardiac disease causes chronic kidney disease. In the third category, abrupt worsening of renal function brings about acute cardiac dysfunction, whereas, in the fourth subcategory, chronic renal disease causes chronic cardiac disease in the form of hypertrophy. However, a single pathology may affect both the heart and kidneys at the same time, and this is also a discrete subcategory[3].

Levosimendan, a calcium sensitizer, has been introduced for the treatment of acute and chronic HF[4-6]. Because there is a significant impact of impaired renal function on the prognosis of HF, an ideal inotrope is expected to improve not only the cardiac output, but also the cardiorenal syndrome. Levosimendan differs from conventional inotropes with its

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renal-enhancing effects[7]. The potential beneficial effects of levosimendan in patients with HF and impaired renal function could be due to the increase in renal blood flow, levosimendan-induced vasodilatation mediated by the blockade of ATP-sensitive potassium channels, the alteration of mesangial cell contraction with a consequent increase in glomerular capillary surface area, or anti-inflammatory effects against the possibility of tubular injury[8-11]. However, it is not well understood that whether this beneficial effect is related to renal status, which could either be in the form of acute worsening of renal function or established and long standing impairment of renal function, during index event or not. In the current study, we aimed to determine whether or not a difference existed in the renal-enhancing effect of levosimendan in patients with and without worsening renal function.

Materials and Methods

The study protocol, which included investigation of all heart failure patients who were administered levosimendan between January 2007-December 2009, was approved by the local Ethics Committee and all subjects gave informed consent. One hundred forty-four consecutive patients with severe, low-output, acute decompensated systolic HF (ejection fraction [EF] <35%, all patients were New York Heart Association [NYHA] class IV), who were administered inotropic therapy with levosimendan based on the discretion of their primary physicians, were evaluated retrospectively. The patients were excluded from the study for the following reasons: administration of inotropic therapy on the day of hospitalization (n=37); history of acute coronary syndrome or cardiogenic shock within the last month prior to the index hospitalization (n=6); prescription of potentially nephrotoxic drugs within the month before hospitalization (n=2); severe primary valvular disease (n=4); lack of at least 2 consecutive follow-up data regarding renal function before and after the infusions (n=7); being under renal replacement therapy before hospitalization (n=5); history of end-stage renal disease (n=12); and normal GFR (glomerular filtration rate >90 ml/min/m^2) prior to administration of levosimendan (n=26). The GFR was estimated for each patient according to the Modification of Diet in Renal Disease (MDRD) formula[12].

Data of 45 consecutive patients who had acute decompensated HF and impaired renal function (GFR <90 mL/min/m^2) with at least two consecutive data regarding renal function during the index hospitalization prior to administration of levosimendan, were considered for the analysis. The creatinine levels for all patients were obtained from the medical records of the patients. Worsening renal function was defined as an increase in the serum creatinine level by ≥0.3 mg/dL from a stable baseline level within the last 1 month during the index hospitalization[13]. Patients who did not have an apparent exacerbation of HF, with fluctuating creatinine levels >0.3 mg/dL within the last 1 month (without considering the levels measured in the hospital), were excluded. Authors thought that levosimendan-induced hypotension would increase tubular injury and that would affect the results. Because of that, patients who were at risk for hypotension (blood pressure were lower than 90/50 mmHg in the beginning of hospitalization) were also excluded from study. Thus, only patients with worsening renal function related to the index exacerbation of HF were considered. Patients were classified into two groups, as follows: (1) those with worsening renal function who were considered to have type I cardiorenal syndrome[3], which was defined as an acute kidney injury upon acute deterioration of cardiac function, and (2) those without worsening renal function prior to administration of levosimendan. Serial measurements of serum creatinine levels were performed. The most recent creatinine level measured prior to levosimendan infusion was accepted as the baseline value. Levosimendan was initiated with a 30-minute bolus of 3-12 μg/kg/min, followed by a 24-hour infusion of 0.1 μg/kg/min, and up-titrated to 0.2 μg/kg/min if tolerated by the patient. Renal function was evaluated 48-72 hours after the infusion (the last available record between these periods during which the dose of other drugs were not changed). During this period, the dosages of all drugs including diuretics were constant. Patients with physician-ordered changes of active drugs (Table 1) were excluded (patients who had already been excluded due to end-stage renal disease, renal replacement therapy and use of nephrotoxic drugs). The patient flow chart was presented in Figure 1.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (Version 10.0; SPSS, Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation, or as n (%), as applicable. Parametric data were evaluated by the Mann-Whitney U test. Temporal changes in parametric data were evaluated by the Wilcoxon signed rank test for paired samples. Categorical data were evaluated by a chi-square test. A p value ≤ 0.05 was considered statistically significant.

Results

The baseline characteristics of the patients are presented in Table 1. There were no significant differences between patients with and without worsening renal function with respect to age, gender, blood pressure, baseline serum creatinine and GFR level, and frequency of hypertension, diabetes mellitus, and atrial fibrillation. The patients with and without worsening renal function received furosemide, the only currently available loop diuretic in Turkey, at a median dose of 80 mg/day the day before and after infusion.

In the overall study sample, a slight but significant improvement was noted in the GFR levels after levosimendan infusion (52.18±16.8 to 55.3±22 mL/min/m^2, p=0.05). In patients with worsening renal function, the levosimendan infusion led to a significant improvement in the serum creatinine level (1.4±0.16 to 1.21±0.23 mg/dL, p=0.001), as well as in the GFR level (48.9±15 to 59.3±21.8 mL/min/m^2, p=0.011). However, there was no significant difference between the creatinine and GFR levels measured at baseline and after infusion in those without worsening renal function (1.29±0.33 to 1.37±0.66 mg/dl, p=0,240 and 53.7±17.6 to 52.9±21.4 mL/min/m^2, p=0.850, respectively; Table 2).

A significant difference was noted between the patients with and without worsening renal function with respect to an absolute change in creatinine and GFR levels (-0.19±0.16

Table 1 - Baseline characteristics of the patients with and without worsening renal function

	Patients with worsening renal function (n=14)	Patients without worsening renal function (n=31)	p
Age (years)	65.5±7.32	66.16±9.17	0.814
Gender (male/female)	11/3	24/7	0.931
Hypertension (n, [%])	13 (92.8)	25 (80.6)	0.407
DM (n, [%])	8 (57.1)	13 (41.9)	0.344
AF (n, [%])	6 (42.8)	11 (35.5)	0.744
Baseline heart rate (beats/min)	90±15	84±14	0.176
Systolic BP (mmHg)	110±14	104±14	0.246
Diastolic BP (mmHg)	69±10	68±10	0.794
Baseline EF (%)	25±6	25±9	0.966
Baseline SPAP (mmHg)	57±4	49±16	0.530
BUN (mg/dL)	31±8	30±9	0.678
Baseline creatinine level (mg/dL)	1.40±0.16	1.29±0.33	0.110
Baseline GFR level (mL/min/m2)	48.9±15	53.7±17.6	0.384
Beta blocker use (n, [%])	12 (85.7)	26 (83.9)	0.874
ACE inhibitor use (n, [%])	12 (85.7)	27 (87.1)	0.899

ACE: angiotensin converting enzyme, BP: blood pressure, BUN: blood urea nitrogen, EF: ejection fraction, SPAP: systolic pulmonary artery pressure, AF: atrial fibrillation, DM diabetes mellitus, GFR: glomerular filtration rate

to 0.08±0.4, p=0.017 and 18±16 to 1.9±22, p=0.004, respectively Table 3).

As a result, a significant renal-enhancing effect of levosimendan was observed in patients with HF and worsening renal function, whereas, almost neutral effect was observed in those without worsening renal function.

Discussion

Worsening renal function frequently complicates the course of HF decompensation. Thus, any drug which can improve worsening renal function might affect therapeutic decision, and levosimendan appears to have the potential to reverse worsening renal function. It is traditionally accepted that reduced renal perfusion pressure, primarily a result of decreased mean arterial pressure, is the main determinant of worsening renal function. Patients with worsening renal function, which can be regarded as impaired organ perfusion in the setting of decompensated HF, are usually treated with traditional inotropes with the expectation to increase perfusion pressure primarily. On the other hand, levosimendan with venodilatory properties was shown to be beneficial compared to a traditional inotrope in patients with HF and renal dysfunction, in a study conducted by Yilmaz et al.[7] However, in that particular study, all patients had worsening renal function, and thus there was a lack of evidence suggesting a selective beneficial effect of levosimendan in such patients. In the current study, levosimendan provided a selective beneficial effect in patients with worsening renal function, whereas there was a near-neutral effect in patients without worsening renal function.

In a case-control study in 2009, Yilmaz et al.[5] showed that levosimendan was beneficial in severe systolic HF patients with an accompanying right ventricular dysfunction, which could be the major determinant of increased central venous pressure. In a recent paper, it was shown that central venous pressure was related to worsening renal function, and thus the potential association between the improvement in renal function and levosimendan might be driven by an improvement in right ventricular function (suction effect, partly driven by improved left ventricular function) and an associated decrease in central venous pressure[14]. However, except for the crude markers of cardiac function (dilated right ventricle), patient data regarding right ventricular function (such as longitudinal motion and tissue Doppler findings) during index hospitalization were missing in our study. In fact, the entire study population was noted to have some degree of right ventricular dilatation.

It appears possible that in patients with severe, acute decompensated systolic HF and worsening renal function, timely intervention with levosimendan can reverse the ongoing process of renal dysfunction through several protective mechanisms. In contrast, regardless of its severity, the relatively stable renal dysfunction associated with chronic HF appears to be resistant to any inotropic insult, since it is not an acute pathophysiologic condition resulting in organ hypoperfusion.

Renal function is dependent on renal blood flow and central venous pressure, which is an important and independent predictor of estimated GFR in patients with heart failure. Elevated intravenous pressure might contribute to the increase of renal vein pressure leading to impaired renal function through decreased perfusion pressure for the glomeruli. We think that various effects

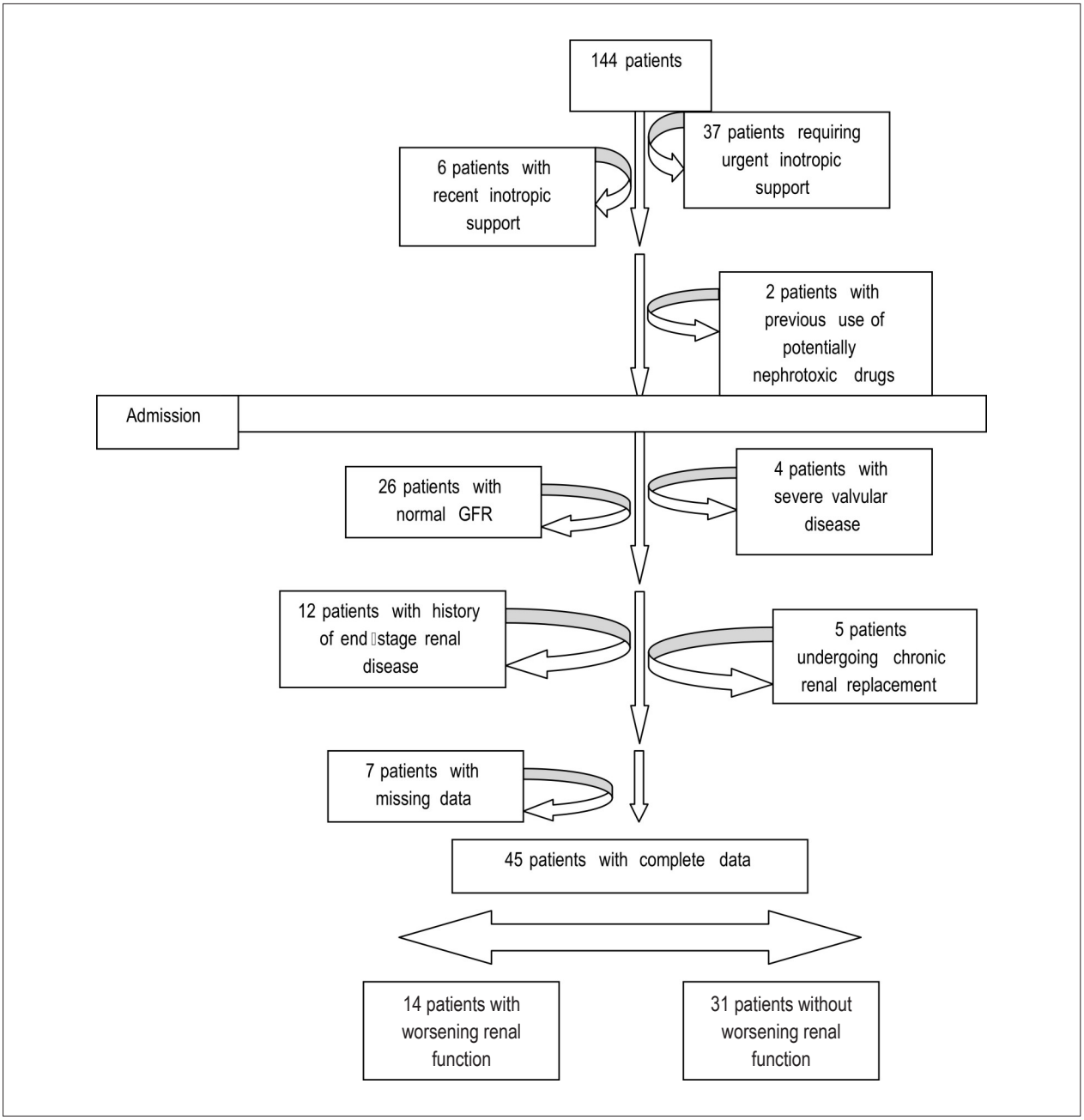

Figure 1 - *Patient flowchart.*

of levosimendan and its metabolites may contribute to the improvement in renal function, such as the increase in renal blood flow due to improved hemodynamic state[15-16], augmentation in renal perfusion via potent vasodilatation through K ATP channel agonism and the reversal of AT-2 mediated mesengial cell contraction causing increase in glomerular capillary surface area[8]. Another possible mechanism is the functional improvement in the right ventricle which probably leads to decrease in central venous pressure. Our prior research[17] showed that levosimendan seemed to provide more beneficial effects among patients with biventricular systolic heart failure, along with decrease in pulmonary pressure and increase in right ventricle contractility, both of which may be acting together up on the net effect. The favorable effects of levosimendan on right ventricle systolic dysfunction might have resulted partially from the improvement of left ventricle function. Finally, one could suggest that the main explanation for this beneficial effect is the venodilatory effects of levosimendan, reducing central venous pressure[18]. There are other studies concerning this subject. One of them[19] analyzed the beneficial effect of levosimendan on the right ventricle diastolic

Table 2 - Parameters of renal and cardiac functions in patients with and without worsening renal function

	Baseline GFR level (mL/min/m²)	GFR level after infusion (mL/min/m²)	p	Baseline creatinine level (mg/dL)	Creatinine level after the infusion (mg/dL)	p	Baseline EF level (%)	EF level after infusion (%)	p
Patients with worsening renal function (n=14)	48.9 ± 15	59.3 ± 21.8	0.011	1.40 ± 0.16	1.21 ± 0.23	0,001	25 ± 6	29 ± 6	0.018
Patients without worsening renal function (n=31)	53.7 ± 17.6	52.9 ± 21.4	0,850	1.29 ± 0.33	1.37 ± 0.66	0,240	25 ± 9	27 ± 6	0.002

GFR: glomerular filtration rate

Table 3 - Temporal changes in creatinine, GFR and EF levels of patients with and without worsening renal function

	Patients with worsening renal function (n=14)	Patients without worsening renal function (n=31)	p
Percent change in GFR[a]	18 ± 16	-1.9 ± 22	0.004
Change in creatinine[b] (mg/dL)	-0.19 ± 0.16	0.08 ± 0.4	0.017
Percent change in EF[c]	11 ± 15	7 ± 11	0.365

[a]Change in the glomerular filtration rate: (GFR after infusion-GFR before infusion)/GFR before infusion; [b]Creatinine after infusion-creatinine before infusion; [c] Change in the ejection fraction: (EF after infusion-EF before infusion)/EF before infusion.

function as well as systolic function. Increased diastolic filling of the right ventricle possibly contributes to decrease in central venous pressure.

On the other hand, there was no correlation between improvement of cardiac functions defined by ejection fraction and improvement serum creatinine levels (p=0.230). This finding also supports authors' hypothesis suggesting that improvement in renal functions was mainly due to peripheral effects of levosimendan rather than systolic enhancement.

One of the main limitations of this study is lack of data regarding left ventricle contractility except than ejection fraction. However, ejection fraction is major indicator of cardiac contractility. Although significant increase in ejection fraction after levosimendan was noted in all patients, only patients who had baseline renal impairment showed a significant decrease in serum creatinine levels.

The difference might be driven by worse creatinine levels at admission, because, the worse it is at admission, the better it is the improvement in general. However, it is of note that all patients in the current study had impaired renal function, indicated by a GFR <90 ml/min/m². Furthermore, more precise definitions for renal dysfunction with new markers indicating early injuries could increase the possible impact of acute therapy since creatinine is a relatively late marker of renal injury[20]. This was the logic for considering creatinine records 48-72 hours after the infusions, but before any change in drugs with the potential to influence renal function. Earlier samples might have underestimated the changes due to the relatively delayed effect on creatinine. On the other hand, enrollment of all patients with worsening renal function irrespective of the issue whether the renal function of the patient deteriorated during the hospitalization or before the hospitalization might be criticized, because, pathophysiologically speaking, these two may be different. Some may criticize the use of levosimendan in patients with impaired renal function. Of note, none of the patients was in end-stage renal disease, although levosimendan has been proven safe and effective in such patients.

Limitations

There were several limitations to the current study. First of all, the retrospective nature of data handling is subject to a number of confounders, including possible effects of uncontrolled drugs and acute hemodynamics (hypotension-hypertension). In addition, we were not able to evaluate the impact of central venous pressure since data regarding central venous pressure and parameters of right ventricular function were not available in the medical records of the patients, although it is known that central venous pressure significantly affect renal perfusion pressure, and thus the GFR[14].

Although, the findings of our study were in accordance with the recent literature[21-24], the small sample size and the lack of a comparable inotrope, which could have potentially increased the confounders, prevented us from drawing

definitive conclusions. However, we performed a post hoc power analyses baseline and after the infusion creatinine levels in patients with and without worsening renal function. We calculated a power of 80.29 % with a $p < 0.05$ and our case numbers in the study groups. However, it is of note, no study has considered this point so far. Thus, there is a need for prospective comparative studies on renal-enhancing effects of levosimendan in patients with and without worsening renal function.

Conclusion

In conclusion, renal-enhancing effects of levosimendan, indicated by the percent change in GFR and a change in creatinine, in patients suffering from severe, acute decompensated systolic HF seems to be restricted to patients with worsening renal function. However, we think we need further studies to prove the concept.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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