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Levosimendan Improves Renal Function in Patients with Acute Decompensated Heart Failure: Comparison with Dobutamine

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Abstract
Background Levosimendan is a relatively new cardiac inotropic agent with calcium sensitizing activity. This study was conducted to investigate the effects of levosimendan (L) and dobutamine (D) on renal function in patients hospitalized with decompensated heart failure (HF).
Method The present study included 88 consecutive patients hospitalized with acutely decompensated HF (New York Heart Association (NYHA) Class 3–4) requiring inotropic therapy. Patients were randomized 2:1 to either L or D for intravenous inotropic support. Diuretic therapy was kept constant during infusions. Renal function values, including serum creatinine (CR), blood urea nitrogen, 24-h urinary output levels and calculated glomerular filtration rate (GFR) were measured just prior to and 24 h after the infusions in all patients, and 48 and 72 h after the infusions in every second patient in both groups. The pre and post-infusion values of renal function and left ventricular ejection fraction (LVEF) were evaluated.
Results LVEF increased significantly in both groups. Those in L showed a significant improvement in calculated GFR after 24 h, whereas those in D showed no significant change (median in change in L:+15.3%, median change in D: −1.33%). Furthermore, in the L group a significant improvement was observed in calculated GFR after 72 h compared to baseline levels, whereas in D no significant change (median change in L:+45.45%, median change in D: +0.09%) was seen. Both agents improved 24-h urinary output.
Conclusion Levosimendan seems to provide beneficial effects in terms of improvement in renal function compared to dobutamine in patients with heart failure who require inotropic therapy.

Key words levosimendan · dobutamine · heart failure · renal function · glomerular filtration rate

Introduction

Moderately elevated blood urea nitrogen and creatinine levels are often encountered in congestive heart failure (CHF) secondary to reductions in renal blood flow and glomerular filtration rate (GFR) [1]. Levosimendan (L) is a relatively new cardiac inotrope introduced for treating acute and chronic congestive heart failure [2, 3]. An ideal inotrope is expected not only to improve cardiac output to provide increased renal blood flow but also to provide ancillary renal benefits. L might be different in terms of renal enhancing effects compared to conventional inotropes. This study was conducted to evaluate and compare the effects of L and dobutamine (D) on renal functions and 24-h urinary output levels in patients with advanced congestive heart failure (HF).

Materials and methods

One hundred consecutive patients with severe low-output systolic HF (NYHA III–IV) and a left ventricular ejection fraction (EF) ≤40%, hospitalised with a diagnosis of acutely

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decompensated HF, for whom inotropic therapy was needed on the judgement of their primary physician, were referred to our study. As soon as the decision to administer the inotrope was made, initial screening for inclusion was done within 1 h. Inclusion criteria were: (1) at least 24 h hospitalization; (2) determination of urine output prior to referral for inotropic therapy; (3) presence of parameters of renal function before inotropic therapy. Hence, eight patients who were referred to inotropic therapy less than 24 h after hospitalization, and four patients with unavailable data were excluded. Eighty eight patients were randomized in a 2:1 ratio to either levosimendan (group L, n=58) or dobutamine (group D, n=30). L was administered for 24 h, initially at a rate of 0.1 μg/kg/min, with uptitration to 0.2 μg/kg/min after 6 h of infusion if tolerated. L loading was left to the judgement of the primary physicians. D was administered for at least 24 h, initially at a rate of 5 μg/kg/min for at least 6 h, after which it was up to the attending primary physicians to increase the dose after 6 h or to administer longer than 24 h. During the infusions, the diuretic dose remained unchanged and no change in the intravenous fluid administration was allowed. Also, nephrotoxic agents were not allowed. Other drug therapy and the decision to discharge, determined by the status of the patients, were left to the physicians, who were blinded to the study outcomes, including clinical parameters. Patients with acute inflammatory diseases, recent myocardial infarction (within 2 months) or acute coronary syndromes, severe hepatic disease (ALT>5 times upper limit of normal), and those who used nephrotoxic drugs within the last month including nonsteroid anti-inflammatory drugs other than low dose aspirin, were not included into the study. Echocardiographic examination was performed using available ultrasound equipment (GE-Vivid 4 with a 3.5 MHz transducer, Wisconsin, USA) at baseline and again 24 h after the administration of both agents. EF was measured by Modified Simpson's rule. Parameters of renal function including serum creatinine, blood urea nitrogen and 24-h urinary output levels were measured just prior to and 24 h after the infusions in whole study group. Every second patient was enrolled into further follow up for renal function and urinary output levels after 48 and 72 following infusions. Glomerular filtration rate (GFR) was calculated by MDRD formula for each patient [4]. The pre and post-infusion parameters of renal function were compared with each other.

Statistical analysis

Parametric data were expressed as mean ± standard deviation, and categorical data as percentages. SPSS 10.0 (SPSS, Inc., Chicago, Illinois) was used to perform statistical procedures. Parametric data were evaluated by independent sample's t test. Temporal changes in parametric data were evaluated by paired sample t test for only paired samples and categorical data via chi square test. A p value$\leq$0.05 was accepted significant.

Results

The mean age of the whole study group was 65.5± 10.2 years (75 males, 13 females). The most frequent etiology was ischemic cardiomyopathy (74 out of 88 patients) and nonischemic nonvalvular cardiomyopathy in the remaining patients. Mean ages in the L and D groups were not different, nor the division in sex or etiology (Table 1). All patients were on optimal doses of ACE inhibitors or angiotensin receptor blockers before, during and after both infusions. Since nesiritide is not available in our country, no patient received it. Forty seven patients in L and 23 patients in D were on beta blocker therapy (p= 0.567). The median dose of loop diuretic (in the form of

Table 1 Comparison of levosimendan and dobutamine groups

	Levosimendan (n=58)	Dobutamine (n=30)	p
Age (years)	65.7±10.6	65.1±9.5	0.641
Sex (male/female)	50/8	25/5	0.719
Basal creatinine (mg/dl)	1.58±0.56	1.41±0.41	0.112
Basal blood urea nitrogen (mg/dl)	46±18	49±24	0.673
Basal 24-h urine output (ml)	1,054±441	1,066±373	0.899
24-h urine output after 24 h of infusions (ml)	1,947±870	1,920±599	0.878
Basal calculated glomerular filtration rate (ml/min/1.73 m2)	51.5±22.1	54.7±19.7	0.511
Calculated glomerular filtration rate after 24 h of infusions (ml/min/1.73 m2)	58.6±21.9	52.2±16.3	0.123
Systolic BP before infusion (mmHg)	106±11	105±9	0.681
Diastolic BP before infusion (mmHg)	73±10	76±7	0.216
Systolic BP after infusion (mmHg)	101±12	104±10	0.189
Diastolic BP after infusion (mmHg)	71±12	72±11	0.347

furosemide) was 60 mg/day in both groups and kept constant up to 72 h in all patients. All patients received L at the suggested dose for 24 h. Sixteen patients in D had 72 h infusion of D, eight patients had 24–48 h infusions, and six patients had 24 h infusion of D. The median dose of D was 7.5 μg/kg/min. Fourteen patients in D and 27 patients in L had longer follow-up periods (>24 h). Blood pressure levels were not different between the two groups before and after infusions (Table 1). However, in the L group, systolic blood pressure decreased significantly following infusion (p=0.026).

Changes in GFR

Baseline EF was similar in both groups (L: 20±3 % vs. D: 20±4 %, p=0.496) and it improved almost to the same extent in both groups (L: 25±4 % vs. D: 24±6 %, p=0.386) during the second echocardiographic examination at 24 h of both infusions. Both groups were comparable in terms of creatinine, blood urea nitrogen, urine output, and calculated GFR before the infusions (Table 1). When median percent change in calculated GFR was considered comparing baseline levels after 24 h and levels after 72 h, respectively, significant differences were observed. Median changes in calculated GFR after 24 h were significantly greater in L compared to D (L:+15.3%, vs. D: −1.33%, respectively, p< 0.001). Furthermore, the median change in calculated GFR after 72 h compared to baseline levels was significantly greater in L than in D (L:+45.45% vs. D: 0.09%, respectively, p<0.001). Thus, L provided net positive changes in GFR, whereas those of D were almost neutral. In accordance with this finding, patients in L had a significant improvement in their calculated GFR from baseline to after 24 h (n=58, all patients in L, from 51.5±22.1 to 58.6± 21.9 ml/min/1.73 m2, p<0.001), and from baseline to after 72 h (here only follow up patients were considered, n=27, from 47.2±24.1 to 65.5±30.4 ml/min/1.73 m2, p<0.001). On the other hand, patients in D had no significant changes in their calculated GFR levels after 24 h of infusion [n=30, from 54.6±19.7 (baseline) to 52.2±16.3 (24 hours)ml/min/ 1.73 m2, p=0.118], and also no significant change in their calculated GFR levels after 72 h [only follow up patients were considered, n=14, from 53.8±25.7 (baseline) to 54.8± 23.7 (72 h) ml/min/1.73 m2, p=0.324]. Hence, the calculated GFR gradually and significantly increased in L, whereas no significant changes were observed in D during the entire study (Fig. 1).

Changes in urine output

In the L group, 24-h urine output increased from the pre-infusion mean level of 1,054±441 ml to 1,947±870 ml at 24 h after L infusion (p<0.001). In the follow up group of L (n=27), 24-h urine output increased from pre-infusion level of 1,269±532 ml to 2,535±865 ml at 48 h after L infusion (p<0.001), and to 1,994±609 ml at 72 h after L infusion (p<0.001).

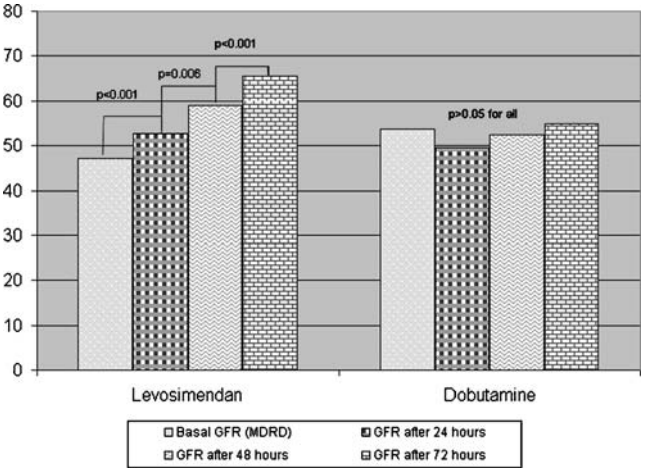

Fig. 1 Temporal change of glomerular filtration rate in the follow up group (n=27 in levosimendan, n=14 in dobutamine). Vertical axis denotes for calculated glomerular filtration rate by MDRD formula

In the D group, 24-h urine output increased from a pre-infusion mean value of 1,066±373 ml to 1,920±599 ml after 24 h of D infusion (n=30, p<0.001). In the follow up group of D (n=14), 24-h urine output increased from a pre-infusion level of 1,220±453 ml to 1,821±523 ml at 48 h after D infusion (p<0.001), and to 1,523±295 ml at 72 h after D infusion (p=0.027).

Discussion

Systolic CHF is characterized by compensatory hemodynamic alterations including salt and water retention, vasoconstriction and neurohormonal, e.g. sympathetic stimulation that may affect various organ systems adversely in the long-term. In addition to renal hypoperfusion, secondary to pump failure and redistribution of blood flow to vital organs (brain etc.), intra-renal vasoconstriction may also play a role in the reduction of renal perfusion in the later stages of CHF. Intra-renal vasoconstriction is generally caused by activation of the renin angiotensin pathway, increased vasopressin, endothelin and catecholamine production and increased renal sympathetic tone [5]. As a consequence, the classic ‘prerenal’ form of renal failure occurs [6, 7, 8]. If the reduction in renal perfusion becomes constant and severe, another form of renal failure termed ischemic tubular necrosis may supervene. In an animal model, it was shown that HF predisposed to outer medullary tubular injury, which was thought to have an important role in the pathogenesis of acute tubular necrosis

[9]. In CHF, increased cytokine levels, such as TNF alfa, may lead to overexpression of inducible nitric oxide synthase (NOS 2), which then results in huge amounts of circulating NO. Large amounts of NO may worsen tubular injury either via caspase activation [10] or conversion to peroxynitrite, a potent reactive oxidant [11].

L is a phospodiesterase inhibitor with myocardial calcium sensitizer activity. Due to its metabolytes (OR-1855, OR 1896), L may lead to constant and prolonged effects. The actions of L and its metabolytes raise the possibility that they may confer reno-protective benefits such as: (a) an increment in renal blood flow due to the hemodynamic improvement [12, 13]. (b) additional augmentation of renal perfusion via potent vasodilation [14, 15] through K-ATP channel agonism. (c) reversal of AT-2 mediated mesangial cell (MC) contraction with consequent increase in glomerular capillary surface area and GFR, and (d) possible anti-inflammatory properties [16, 17] suggesting that it may protect against tubular injury. L is reported to confer marked protection against endotoxemic acute renal failure (EARF), a complication of gram negative sepsis [18]. Cytokine and NO production in response to lipopolysaccaride (LPS) appear to play a central role in EARF. In general, L was found to be effective due to its GFR enhancing effects rather than its anti-inflammatory properties in EARF.

Although some studies indicate that doses of L should be reduced in CHF patients with severe renal failure [19], some reports [20] recommend gradual increments in infusion rate to increase its tolerability in severe renal failure. L is generally well tolerated without the need of dose reduction in patients with moderately impaired renal function. Beyond this, renal function may also be improved in this group of patients with CHF (as in the present study) through the GFR enhancing effects of L.

In the present study, L infusion yielded a significant net improvements in GFR compared to D, though both increased in urine output. Actually, findings associated with calculated GFR were in accordance with an old study, stating that dobutamine did not provide any renal enhancing effect [21]. Our results are also in accordance with a recent study [22] that showed that intravenous inotropes, other than L, did not have any effect on renal function [22]. The increase in urine output with D in our study does not prove that D has a beneficial effect on renal function per se. Our study group consisted of patients with acutely decompensated systolic HF with significant degrees of fluid overload (median pretibial edema was ++/++ for each group). Hence, D might have resulted in moving the congested fluid by its cardiac enhancing activity alone. While this might be true for L as well, there should be other mechanisms to explain the increase in GFR as well as urine output in the L group. Of note, these changes were observed despite a constant diuretic dose and constant amount of intravenous fluid administration before (median 1,000 ml for each group) and 72 h after the infusions. Furthermore, this improvement in renal function persisted for at least another 2 days after the 24 h infusion of L, in contrast to D.

Our study is limited by its relatively small study population, and hence, there is a need for further consideration with larger groups. However, our study does, to our best knowledge, provide the first report on parameters of renal function as they relate to the use of L along with concomitant standard HF therapy. Furthermore, considering the long term effects of L and its metabolites, it is worth investigating if there is any longer term renal enhancing effect beyond the period used in this study. A further limitation may be that baseline GFR in the L group was slightly lower (although not significant) than in the D group. Although not very likely in view of the small difference at baseline, it could be argued that the lower initial renal function in the L group may have resulted in a larger benefit (Table 1).

In conclusion; we have shown that levosimendan infusion provides significant improvements in renal function in patients with severe systolic CHF requiring inotropic support compared to dobutamine.

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