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Effect of Levosimendan on Renal Outcome in Cardiac Surgery Patients With Chronic Kidney Disease and Perioperative Cardiovascular Dysfunction: A Substudy of a Multicenter Randomized Trial

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TITLE

Effect of levosimendan on renal outcome in cardiac surgery patients with chronic kidney disease and perioperative cardiovascular dysfunction. A substudy of a multicenter randomized trial

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ABSTRACT

Introduction: Acute kidney injury (AKI) occurs frequently after cardiac surgery, particularly in patients with chronic kidney disease (CKD). Patients with CKD are also at increased risk for mortality and non-renal complications, particularly when glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m^2. Patients undergoing mitral valve surgery are considered as having the highest risk

Methods: This was a post-hoc analysis of a multicenter, placebo-controlled, double-blind, randomized trial. We included a total of 90 patients undergoing mitral valve surgery with estimated GFR < 60 mL/min/1.73 m^2 and perioperative myocardial dysfunction randomized to receive levosimendan or placebo on top of standard inotropic treatment. Primary outcome for this post-hoc study was incidence of postoperative AKI. Secondary outcomes were 30-days and 180-days mortality, need for renal replacement therapy, and change in serum creatinine levels.

Results: A total of 46 patients were assigned to receive levosimendan, and 44 to receive placebo. Primary outcome occurred in 14 (30%) patients in the levosimendan group versus 23 [52%] in the placebo group (absolute difference = -21.8; 95% confidence interval [CI] -41.7 to -1.97; p = 0.035). Incidence of major complications was also lower (18 [39%] in the levosimendan group versus 29 [66%] in the placebo group; absolute difference = -26.8 [-46.7 to -6.90]; p = 0.011). A trend towards lower serum creatinine at ICU discharge was observed (1.18 [0.99 – 1.49] mg/dL in the levosimendan group versus 1.39 [1.05 – 1.76] mg/dL; 95% CI -0.23 [-0.49 to 0.01]; p = 0.07)

Conclusions: Levosimendan may improve renal outcome in cardiac surgery patients with CKD undergoing mitral valve surgery who develop perioperative myocardial dysfunction. Results of this exploratory analysis should be investigated in future properly designed RCTs.

KEY WORDS

INTRODUCTION

Acute kindey injury (AKI) occurs frequently after cardiac surgery and is associated with increased morbidity, mortality, and healthcare-associated costs [O'Neal 2016 Crit Care, Lysak 2017 Curr Opin Anaesthesiol]. Chronic kidney disease (CKD) is common among cardiac surgery patients, as kidney and cardiovascular disease frequently coexists [Go 2004 N Engl J Med, Löfman 2017 Eur J Heart Fail], and is associated with a worse perioperative outcome [Lysak 2017 Curr Opin Anaesthesiol, Hedley 2010 Heart Lung Circ, Ju 2017 Int J Cardiol, Cooper 2006 Circulation]. Not surprisingly, risk of AKI and need for renal replacement therapy (RRT) is particularly high in patients with CKD and in those developing postoperative acute cardiovascular dysfunction [Petaja 2017 J Cardiothorac Vasc Anesth, Pannu 2016 CMAJ, Haase-Fielitz 2017 Blood Purif]. Risk of adverse outcome increase significantly when glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m^2 [Van der Velde 2011 Kidney Int]. Unfortunately, no pharmacologic strategy proved effective in preventing or reducing AKI severity [Di Tomasso 2016 F1000Res].

Levosimendan, a calcium sensitizer with inodilatory effect, has been shown in meta-analyses of randomized controlled trials (RCTs) to reduce incidence of AKI and need for RRT in critically ill and cardiac surgical patients [Bove 2015 Heart Lung Vessel, Zhou 2016 Am J Kidney Dis]. Proposed mechanism of action of levosimendan-related kidney protection include improvement in systemic hemodynamics (increased cardiac output, reduced central venous pressure), improvement in renal hemodynamics (vasodilation of afferent arteriole) and direct cytoprotective, anti-inflammatory and anti-apoptotic effects [Yilmaz 2013 Cardiovasc Drugs Ther, Farmakis 2016 Int J Cardiol]. Levosimendan might be particularly effective in patients with GFR < 60 mL/min/1.73 m^2 [Mehta 2017 N Engl J Med] and in those undergoing mitral valve surgery, which are considered at high risk of postoperative AKI [Bove 2004 J Cardiothorac Vasc Anesth, Baysal 2014 J Cardiothorac Vasc Anesth].

Results of a multicenter RCT on levosimendan use in patients with perioperative cardiovascular dysfunction after cardiac surgery (Levosimendan to Reduce Mortality in High Risk Cardiac Surgery

Patients: A Multicenter Randomized Controlled Trial [CHEETAH]) has been recently published [Landoni 2017 N Engl J Med]. We have therefore decided to perform a post-hoc analysis of the CHEETAH trial to investigate the effect of levosimendan on mortality and renal outcome in patients with eGFR < 60 mL/min/1.73 m^2 undergoing mitral valve surgery.

METHODS

This is a post-hoc analysis of a multicenter, randomized, double-blind, placebo controlled trial performed in 14 centers in Italy, Russia and Brazil. The trial was approved by Ethics Committee of all participating centers and registered on ClinicalTrials.gov with registration no. NCT00994825. Details on CHEETAH study design, procedure, and statistical analysis have been previously published [Landoni 2017 N Engl J Med , Zangrillo 2016 Am Heart J].

Briefly, all patients scheduled for cardiac surgery were assessed for eligibility, and provided written informed consent. Patients were than randomized if they met inclusion criteria either in operating room (OR) or in the intensive care unit (ICU). Patient were included if they required perioperative hemodynamic support, defined as preoperative left ventricular ejection fraction (LVEF) < 25%, preoperative need for intra-aortic balloon pump (IABP), need for high-dose inotropic drugs (defined as vasoactive-inotropic score ≥ 10) or IABP during weaning from CPB or within 24 h from surgery. Exclusion criteria were a previous adverse response to levosimendan, inclusion in another randomized trial, receipt of levosimendan in the previous 30 days, receipt of a kidney or liver transplant, liver cirrhosis, emergency operation, a decision to use extracorporeal membrane oxygenation (ECMO) already made, or the presence of a do-not-resuscitate order.

Patients were randomized (1:1 ratio) to receive levosimendan or placebo, in addition to standard inotropic care. Levosimendan was administered as continuous infusion, with a starting dose of 0.05 µg/kg/min. Dose could be than titrated from 0.025 to 0.2 µg/kg/min at discretion of the attending physician, and continued for up to 48 h.

In this post-hoc analysis, patients with preoperative CKD undergoing mitral valve surgery were included. Preoperative CKD was defined as eGFR < 60 mL/min/1.73 m^2 [Mehta 2017 N Engl J Med, Van der Velde 2011 Kidney Int]. Estimated GFR was calculated using the Modified Diet in Renal Disease (MDRD) equation [Levey 2006 Ann Intern Med].

For this post-hoc analysis, primary outcome was incidence of AKI, defined according to the Risk-Injury-Failure-Loss-End-stage renal disease (RIFLE) classification [Bellomo 2004 Crit Care]. As this was a study focusing on acute care setting, only data on Risk, Injury and Failure stages were collected. Secondary outcomes included 30-days mortality, 180-days mortality, need for RRT, a composite of 30-days mortality and need for RRT. As in the overall population a trend towards reduced incidence of major complications (myocardial infarction, AKI, type 1 and type 2 neurologic damage [Roach 1996 N Engl J Med], septic shock [Dellinger 2008 Intensive Care Med], pneumonia and mediastinitis [Horan 2008 Am J Infect Control]) was observed [Landoni 2017 N Engl J Med], this composite outcome was also analyzed. Finally, we collected and analyzed baseline (preoperative) serum creatinine value, peak serum creatinine in ICU, and serum creatinine value at ICU discharge.

Statistical analysis

Details on sample size calculation and statistical analysis has been described in details previously [Zangrillo 2016 Am Heart J, Landoni 2017 N Engl J Med].

All analyses comparing levosimendan and placebo were performed according to the intention-to-treat principle, and no imputation for missing data was applied.

Data are presented as means ± standard deviation (SD) when the variables were normally distributed or as medians and interquartile ranges (IQR) for non-normally distributed variables. Dichotomous data were compared by 2-tailed χ^2 tests with the Yates correction or Fisher's exact tests when appropriate. The primary analysis was not adjusted for covariates. Continuous measurements were compared using the Mann-Whitney U test.

All reported p-values are 2-sided. Data were stored electronically and analyzed with Stata (Stata Statistical Software: release 13, StataCorp LP, College Station, Texas).

RESULTS

Of 4725 patients who provided written informed consent, a total of 506 patients were enrolled and randomized in the CHEETAH study between November 2009 and April 2016 [Landoni 2017 N Engl J Med]. Preoperative data for eGFR calculation were available for 499 patients. Of these, 187 had a baseline eGFR < 60 mL/min/m^2, with 90 patients undergoing mitral valve surgery and included in the (46 randomized to levosimendan and 44 to placebo).

Baseline eGFR was similar (49.9 [41.0 – 55.3] mL/min/m^2 in the levosimendan group versus 50.2 [42.7 – 55.0] mL/min/m^2 in the placebo group, p = 0.97). Baseline characteristic for this subgroup of patients are described in Table 3. Mean study drug dose was 0.07 (0.05 – 0.1) µg/kg/min in the levosimendan group versus 0.08 (0.05 – 0.1) µg/kg/min in the placebo group.

In patients with CKD undergoing mitral valve surgery, we observed a reduction in the incidence of AKI (14 [30%] in the levosimendan group versus 23 [52%] in the placebo group; absolute difference = -21.8 [-41.7 to -1.97]; p = 0.035), driven by a reduction in stage-R AKI (Table 4).

In addition, we also observed a reduction in major complications (18 [39%] in the levosimendan group versus 29 [66%] in the placebo group; absolute difference = -26.8 [-46.7 to -6.90]; p = 0.011)

Finally, a trend towards a lower serum creatinine at discharge from ICU was also observed (1.18 [0.99 – 1.49] in the levosimendan group versus 1.39 [1.05 – 1.76] in the placebo group; median difference = -0.23 [-0.49 to 0.01]; p = 0.07) (Table 4).

DISCUSSION

Key findings

In this post-hoc analysis of a mRCT, we found that levosimendan administration in mitral valve surgery patients with CKD and postoperative hemodynamic instability resulted in a reduction in the incidence of AKI and of major complications

Relationship to previous studies

Few previous RCTs investigated the effect of levosimendan on renal function in cardiac surgery, although several trials report renal data as secondary outcome. The three largest trial performed so far on levosimendan use in the perioperative setting (CHEETAH, LEVO-CTS, and LICORN trials) all reported renal outcome data as secondary outcome [Landoni 2017 N Engl J Med, Mehta 2017 N Engl J Med, Cholley 2017 JAMA], and found no difference in the incidence of AKI or need for RRT between levosimendan and placebo groups. However, the LEVO-CTS planned subgroup analyses suggested a possible subgroup effect in patients with different baseline eGFR, with patients with eGFR < 60 having the greatest benefit from levosimendan administration (p for interaction = 0.049)

In the largest trial focusing on renal function, Baysal et al [Baysal 2014 J Cardiothorac Vasc Anesth] randomized 128 patients with left ventricular ejection fraction (LVEF) ≤45% undergoing mitral valve surgery to levosimendan (6 µg/kg loading dose after release of aortic cross clamp, followed by a 0.1 µg/kg/min infusion for 24 h), or placebo. The Authors reported higher postoperative eGFR and lower serum creatinine in the levosimendan group, with no difference in the need for RRT or other major outcomes.

Ristikankare and colleagues randomized 60 patients with LVEF ≤ 50% undergoing on-pump CABG to levosimendan (12 µg/kg loading dose, followed by a 24 h infusion of 0.2 µg/kg/min, starting after anesthesia induction) or placebo [Eriksson 2009 Ann Thorac Surg, Ristikankare 2012 J Cardiothorac Vasc Anesth]. They found no difference in kidney injury biomarkers or incidence of AKI (defined according to RIFLE criteria [Bellomo 2004 Crit Care] over the first five postoperative days, although a trend towards a lower incidence of AKI in the levosimendan group was observed.

There are several possible explanation for the different findings reported by our study and above mentioned trials. Our study enrolled patients with established perioperative myocardial dysfunction, which is a well-recognized risk factor for postoperative AKI. It is possible that, in these patients, the restoration of cardiac output determined by levosimendan could have improved and protected kidney function from further deterioration [Bragadottir 2013 Crit Care Med]. On the contrary, in a cardiac surgical population with no myocardial dysfunction the effect of levosimendan on cardiac output could have been offset by the hypotensive effect of the drug. As mean arterial pressure (MAP) is a key determinant of kidney function [Joannidis 2017 Intensive Care Med], this could in turn have led to neutral results. Secondly, in this subgroup analysis we focused on patients undergoing mitral valve surgery, which is a high-risk population for postoperative AKI [Baysal 2014 J Cardiothorac Vasc Anesth, Bove 2004 J Cardiothorac Vasc Anesth]. The combination of high-risk surgery plus development of perioperative myocardial dysfunction could have led to identification a particularly high risk in which beneficial effects of levosimendan offset its side effects on MAP.

Significance of study findings

Despite promising results from meta-analyses [Pollesello 2016 Int J Cardiol, Landoni 2012 Crit Care Med, Harrison 2013 J Cardiothorac Vasc Anesth], large mRCTs failed in demonstrating a beneficial effect on mortality of either prophylactic [Mehta 2017 N Engl J Med, Cholley 2017 JAMA] or therapeutic [Landoni 2017 N Engl J Med] levosimendan infusion. Our study identified a subpopulation of patients undergoing cardiac surgery which could benefit from levosimendan infusion. Despite improvement in surgical and anesthesiological management, mitral valve surgery still carries a high risk of perioperative adverse events [Pieri 2016 BMC Anesthesiol, Nashef 2012 Eur J Cardiothorac Surg]. Due to ageing of population, and increasing prevalence of ischemic heart disease, the number of patients with both functional and degenerative mitral valve disease is going to increase. As new treatment strategies become available [De Bonis 2016 Eur Heart J], a larger

number of patients with increased age and higher prevalence of comorbidities will undergo mitral valve procedures. It is worth noting that also percutaneous mitral valve procedures carry a high risk of postoperative myocardial dysfunction and cardiogenic shock [Melisurgo 2014 Am J Cardiol, Essandoh 2017 J Cardiothorac Vasc Anesth], which could require levosimendan infusion as treatment. Therefore, results of our study could be useful to guide management not only of patients who underwent conventional mitral valve surgery, but also for patients requiring percutaneous mitral valve procedures. This is particularly true in light of the high cost of the drug [Guidet 2015 Intensive Care Med]. In addition, our findings could help to guide and plan future studies on perioperative levosimendan administration by identifying a specific target population and providing data for sample size estimation.

Strengths of the study and limitations of the study

Our study has several strengths. It is randomized, double-blind and placebo controlled, thereby reducing the risk of selection bias. In addition, we chose a clinically relevant outcome defined according to standard and validated criteria [Bellomo 2004 Crit Care]. It has a simple and easily reproducible protocol, with no deviation from routine with exception of study drug administration, which provide external validity. This is further improved by the multicentric design. Finally, our findings have a strong biological plausibility according to available evidence and previous trials [Yilmaz 2013 Cardiovasc Drugs Ther, Farmakis 2016 Int J Cardiol, Bove 2015 Heart Lung Vessel, Zhou 2016 Am J Kidney Dis].

There are also some limitations. The trial was interrupted early for futility for original primary outcome (30-day mortality). This could have reduced power to detect significant differences in secondary outcomes, including AKI. We cannot exclude that using a more strict protocol for levosimendan, fluids, and concomitant inotropes administration could have led to different results and improved outcome. Finally, we report results of an unplanned subgroup analysis, which carries the risk of being a chance finding.

Conclusions

This unplanned subgroup analysis of mRCT suggested that levosimendan administration in mitral valve surgery patients with chronic kidney disease and perioperative myocardial dysfunction may reduce incidence of AKI and major adverse events. These findings should be considered hypothesis-generating and tested in an adequately designed and powered high-quality mRCT.

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TABLES

Table 1 – Baseline Characteristics

Characteristic*	**Levosimendan (N = 46)**	**Placebo (N = 44)**
	Value	Value
Age, yr — median (IQR)	68 (60 – 76)	68 (63 – 78)
Female sex— no. (%)	26 (57%)	24 (55%)
Weight, kg — median (IQR)	73 (64 – 83)	75 (62 – 85)
Height, cm — mean ± SD	167 ± 9.4	166 ± 8.3
BMI, kg/m^2 — median (IQR)	26 (23 – 28)	25 (23 – 29)
Re-do surgery — no. (%)	13 (28%)	8 (18%)
Myocardial infarction — no. (%)	15 (33%)	14 (32%)
Atrial fibrillation — no. (%)	22 (48%)	23 (52%)
Ongoing cardiogenic shock — no. (%)†	1 (2.2%)	1 (2.3%)
NYHA classification — no. (%)		
➢ I	1 (2.2%)	1 (2.3%)
➢ II	12 (27%)	12 (27%)
➢ III	29 (64%)	29 (66%)
➢ IV	3 (6.7%)	2 (4.6%)
COPD — no. (%)	6 (13%)	5 (12%)
History of stroke/TIA	1 (2.2%)	1 (2.3%)
Peripheral vascular disease — no. (%)	4 (8.7%)	5 (12%)
Diabetes — no. (%)	9 (20%)	8 (19%)
LVEF, % — median (IQR)	50 (35 – 62)	50 (36 – 60)
➢ < 25%	4 (8.9 %)	4 (9.3%)
➢ 25 – 40%	12 (27%)	11 (26%)

➢ > 40%	29 (64%)	28 (65%)
Pre-operative medical therapy		
➢ Angiotensin receptor blocker	5 (11%)	2 (4.6%)
➢ ACE-inhibitors	18 (40%)	23 (52%)
➢ Diuretics	35 (78%)	38 (86%)
➢ Digoxin	7 (16%)	7 (16%)
➢ β-blocker	25 (56%)	31 (70%)
➢ Nitrates	3 (6.7%)	7 (16%)
➢ Amiodarone	7 (16%)	7 (16%)
➢ Ivabradine	3 (6.7%)	1 (2.3%)
➢ Ranolazine	1 (2.2%)	0 (0.0%)
Intraoperative characteristics		
➢ Aortic cross-clamp duration	90.2 ± 41.8	99.1 ± 41.7

ACE = angiotensin-converting enzyme; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; ICU = intensive care unit; IQR = interquartile range; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; NYHA = New York Heart Association; SD = standard deviation; TIA = transient ischemic attack

* p-value > 0.05 for all variables

† defined as a state of end-organ hypoperfusion due to cardiac failure. The definition included hemodynamic parameters: persistent hypotension (systolic blood pressure 80 to 90 mm Hg or mean arterial pressure 30 mm Hg lower than baseline) with severe reduction in cardiac index (<1.8 L/min/m2 without support or 2.0 to 2.2 L/min/m2 with support) and adequate or elevated filling pressure (eg, left ventricular end-diastolic pressure > 18 mm Hg or right ventricular end-diastolic pressure > 10 to 15 mm Hg), measured with a pulmonary artery catheter or assessed by echocardiography[25]

‡Inclusion criteria were not mutually exclusive. We list the first single criterion that led to qualification for the trial

Table 2 – Outcomes

Outcome	Levosimendan (N = 46)	Placebo (N = 44)	Difference (95% CI)	P value
Primary outcome				
Acute kidney injury – no. (%)	14 (30%)	23 (52%)	-21.8 (-41.7 to -1.97)	0.035
➢ Risk*	6 (13%)	12 (27%)	-14.2 (-30.6 to 2.14)	0.09
➢ Injury†	4 (8.7%)	5 (11%)	-2.67 (-15.1 to 9.75)	0.74
➢ Failure‡	4 (8.7%)	6 (14%)	-4.94 (-17.9 to 8.06)	0.52
Secondary outcomes				
Need for RRT – no. (%)	4 (8.7%)	9 (20%)	-11.8 (-26.2 to 2.68)	0.14
Need for RRT or 30-day mortality	5 (11%)	11 (25%)	-14.1 (-29.8 to 1.51)	0.08
Major complications §	18 (39%)	29 (66%)	-26.8 (-46.7 to -6.90)	0.011
➢ Myocardial infarction	4 (8.7%)	3 (6.8%)	1.88 (-9.16 to 12.9)	0.99
➢ Type I neurologic damage	2 (4.4%)	2 (4.6%)	-0.20 (-8.72 to 8.32)	0.99
➢ Type II neurologic damage	7 (15%)	9 (20%)	-5.24 (-21.0 to 10.6)	0.52
➢ Septic shock	1 (2.2%)	1 (2.3%)	0.15 (-6.32 to 6.02)	0.99
➢ Pneumonia	0 (0.0%)	3 (7.1%)	-7.14 (-14.9 to 0.65)	0.11
Mortality				
➢ ICU mortality – no. (%)	3 (6.5%)	3 (6.8%)	-2.96 (-10.6 to 10.0)	0.99
➢ Hospital mortality – no. (%)	3 (6.5%)	6 (14%)	-7.11 (-19.5 to 5.28)	0.31
➢ 30-day mortality – no. (%)	3 (6.5%)	6 (14%)	-7.11 (-19.5 to 5.28)	0.31
➢ 180-days mortality – no. (%)	5 (11%)	9 (21%)	-10.1 (-25.2 to 5.06)	0.19
Serum creatinine, mg/dL – mean ± SD				
➢ baseline	1.29 (1.09 – 1.57)	1.32 (1.09 – 1.55)	-0.04 (-0.18 to 0.13)	0.75
➢ peak in ICU	1.59 (1.22 – 2.25)	2.03 (1.63 – 2.41)	-0.37 (-0.74 to 0.01)	0.10
➢ discharge from ICU	1.18 (0.99 – 1.49)	1.39 (1.05 – 1.76)	-0.23 (-0.49 to 0.01)	0.07

ICU: intensive care unit; RRT: renal replacement therapy

* Increase in serum creatinine (SCr) ≥ 1.5x baseline, glomerular filtration rate (GFR) decrease > 25% from baseline, urine output (UO) < 0.5 mL/kg/h for 6 h

† Increase SCr ≥ 2x baseline, GFR decrease > 50% from baseline, UO < 0.5 mL/kg/h for 12 h

‡ Increase SCr ≥ 3x baseline, SCr ≥ 4 mg/dL, GFR decrease > 75% from baseline, UO < 0.3 mL/kg/h for 24 h, anuria for 12 h

§ Composite of acute kidney injury (any stage), RRT, myocardial infarction, Type I and II neurological damage, septic shock and pneumonia