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Comparison between levosimendan versus beta agonists in preservation of renal function in cardiac surgery patients with low cardiac output syndrome

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ABSTRACT

Background: Post cardiac surgery acute kidney injury (AKI) secondary to postoperative low cardiac output syndrome (LCOS), is a serious complication. Positive inotropic agents are the main line of treatment for LCOS with different degrees of improvement of cardiac function & nephroprotective efficacy Levosimendan is a calcium sensitizer in cardiac muscles, which has a comparable positive inotropic and nephroprotective effects to that of classic beta2 agonists.

Objective: To evaluate the possible nephroprotective effect of levosimendan as compared to beta agonists in cardiac surgery patients with LCOS.

Patients and Methods: It is a prospective, randomized and comparative study conducted at Ain Shams University Hospitals over the period from December 2020 to May 2021. A total of 60 patients with post cardiac surgery low cardiac output syndrome were divided into two groups of 30 patients each. Group A (control) received beta-agonists (dobutamine or adrenaline) and Group B (study) received levosimendan. The incidence of AKI at the diagnosis of LCOS & its progression to renal failure in both groups were assessed.

Results: The incidence of AKI at diagnosis of LCOS postoperative was 30% (n = 9) in each group; 44% of them in the control group (n = 4) developed renal failure at discharge from ICU and none of the study group patients developed renal failure at discharge. At the time of discharge from ICU, the incidence of renal failure in beta-agonist group was 13.3%, while the incidence in the levosimendan group was 0% with statistically significant P value of 0.038.

Conclusion: In comparison to beta-agonists, Levosimendan may have a better nephroprotective effect that plays a role in decreasing the incidence of kidney failure in patients with post cardiac surgery LCOS. A larger randomized, controlled trials are recommended to prove such a beneficial nephroprotective effect and its exact mechanism.

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1. Introduction

Acute kidney injury (AKI) is one of the most common complications (3.5–31%) that follows cardiac surgeries[1] and it can rise the postoperative mortality rate from 8% to 60%[2]. The wide variability of the incidence of post cardiac surgery AKI reported by different studies could be attributed to different criteria used to identify AKI and different population characteristics, especially the functional reserve, age, comorbidities, surgical technique used, and so on[3].

The low cardiac output syndrome (LCOS) is one of the most common predisposing factors to AKI in post cardiac surgery (from 30% up to 70%) and also one of the most serious complications post cardiac surgery, with incidence ranging from 15% to 25%. This syndrome is associated with a mortality rate of 15%, reaching up to 70% in patients who develop cardiogenic shock[4]. The standard treatment for LCOS is the use of inotropic action of beta-agonist agents (adrenaline, dobutamine)[5].

An alternative inotropic effect can be provided by levosimendan (a calcium sensitizer). Levosimendan is an inotropic agent with vasodilatory and protective effects, acting via the calcium channels in cardiac myofilaments. It provides cardioprotection against myocardial ischemia and damage caused by ischemia reperfusion[6,7].

There are correlations between the use of levosimendan and improved glomerular filtration rates[8].

We compared the effectiveness of levosimendan for renal protection to the standard therapy of beta agonists in post cardiac surgery patients.

2. Patients and methods

This prospective, randomized, comparative study was conducted at Ain Shams University Hospitals

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after approval from Faculty of Medicine Ain Shams University Research Ethics Committee (FMASU-REC), over a period of 6 months, from December 2020 to May 2021.

Study was conducted on 60 patients aged 18–75 years old, who underwent cardiac surgery (either on-pump or off-pump) and developed postoperative left ventricular dysfunction (LVEF <50%) and low cardiac output state (systolic blood pressure <90 mmHg and/or signs and symptoms of hypoperfusion (tachycardia, cold periphery, delayed capillary refill, oliguria with UOP <0.5 ml/kg/h, altered mental status and high serum lactate >3 mmol/l) despite adequate filling status or central venous saturation <60% after volume replacement).

Patients were excluded from our study if they sustained preoperative renal dysfunction (creatinine clearance <50 ml/min), preoperative left ventricular dysfunction (LVEF<50%) and emergency surgery.

Sample size was calculated using PASS11 program, setting power at 80% and alpha error at 5%. Reviewing results from previous study[9] showed that 40% of post cardiac surgery patients who developed low cardiac output state (LOCS) and were treated with beta-agonists develop postoperative renal failure, while none of those patients who treated with levosimendan developed renal failure. Based on this, a sample size of atleast 60 patients (30/group) is needed.

2.1. Study procedures

An informed written consent was obtained preoperatively after a simple and informative explanation of the procedure to all patients fulfilling our inclusion criteria and admitted for open heart surgical procedures during the assigned study period (about 200 patients).

In post cardiac surgery ICU, once LCOS was diagnosed (SBP <90 mmHg and/or signs and symptoms of hypoperfusion (tachycardia, cold periphery, delayed capillary refill, oliguria UOP <0.5 ml/kg/h, altered mental status and serum lactate >3 mmol/l) despite adequate filling status or central venous saturation <60% after volume replacement) and LVEF <50% by echocardiography, patients were recruited (60 patients) and allocated to one of the two groups using simple randomization of 1:1 ratio, and treatment was initiated immediately either with beta-agonists (GA) or levosimendan (GB).

Group A (control group): Patients received beta-agonists (dobutamine 2–20 mcg/kg/min or adrenaline 0.01–0.5 mcg/kg/min) and maintained until resolution of LCOS, targeting a central venous O_2 saturation >65% following volume replacement.

In cases with SBP <90 mmHg, adrenaline was used or norepinephrine was added (0.01–0.4 mcg/kg/min).

Group B (study group): Patients received levosimendan for 24 h at a rate of 0.1 mcg/kg/min to a target dose of 12.5 mg. targeting a central venous O_2 saturation >65% following volume replacement.

In cases with SBP <90 mmHg, norepinephrine was added (0.01–0.4 mcg/kg/min).

Patients were continuously monitored with ECG, invasive blood pressure measurement and pulse oximetry.

2.2. Data to be collected

The data to be collected are as follows: demographic data (age, sex, height and weight), risk factors (hypertension, diabetes, smoking and dyslipidemia), type of operation, cardiopulmonary bypass and aortic cross-clamping time if "on pump", hemodynamics (heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP) and central venous O_2 saturation), left ventricular ejection fraction (LVEF)/heart failure stage (as per Killip's classification)[10] at the time of diagnosis of LCOS, renal functions (serum creatinine level, urine output (ml/kg/h), diuretic dose (mg of furosemide) and kidney injury/failure as identified by the acute kidney failure (AKI) score[11] at the diagnosis of LCOS, 24 and 48 h after diagnosis of LCOS and at the time of ICU discharge.

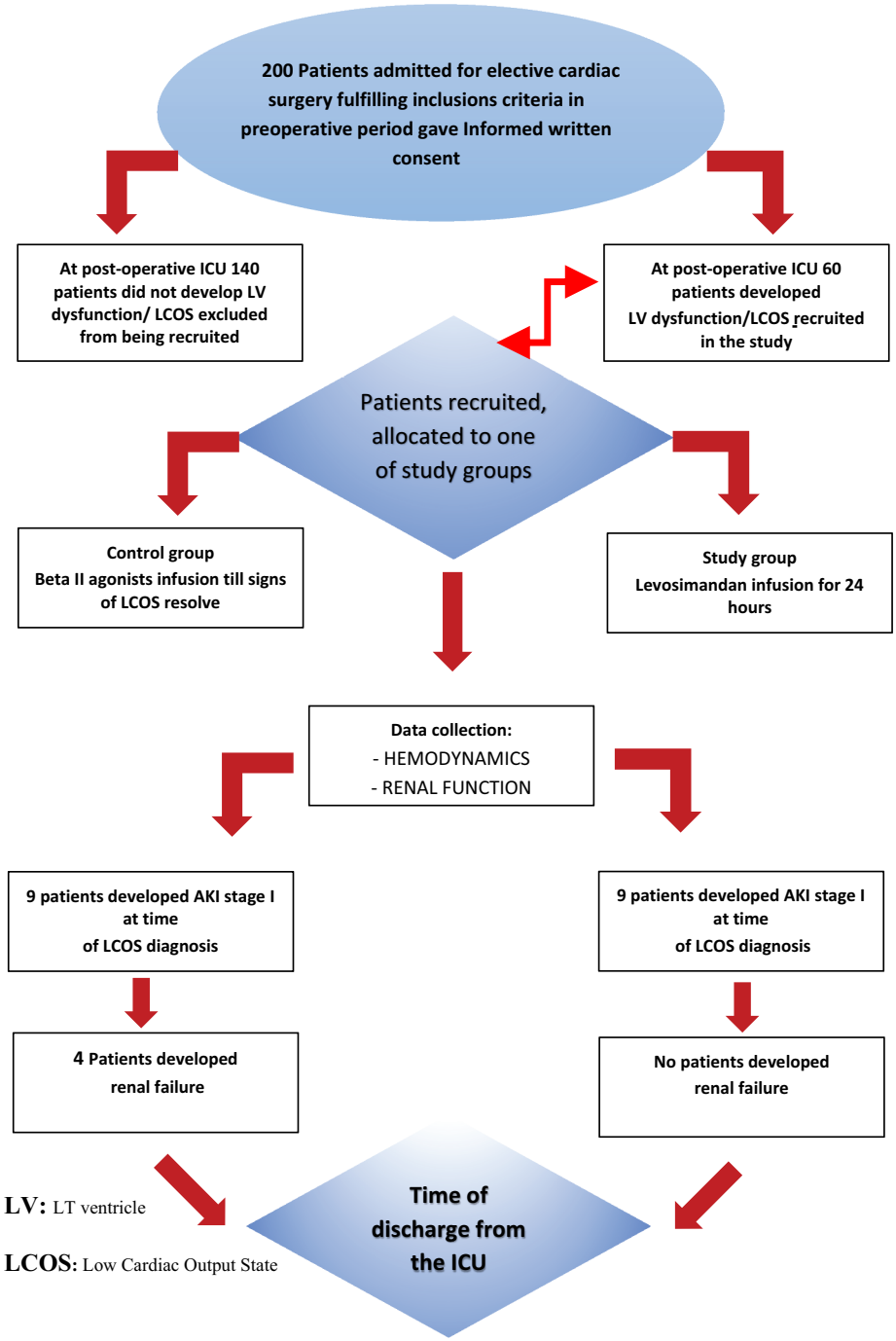
Study primary outcome: The incidence of renal failure (according to AKI scale definition) at time of discharge from ICU.

2.3. Study flow chart

2.4. Statistical analysis

Recorded data were analyzed using the Statistical Package for Social Sciences (SPSS II). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following statistical tests were conducted: Independent-samples t-test of significance was used when comparing between two means. Mann–Whitney U-test was used for two-group comparisons in non-parametric data. Chi-square (X^2) test of significance was used to compare proportions between qualitative



parameters. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. Therefore, the *P*-value was considered significant as the following: *P*-value < 0.05 was considered significant. *P*-value < 0.001 was considered as highly significant. *P*-value > 0.05 was considered insignificant.

3. Results

There were no significant differences between the two groups regarding demographic data, preoperative risk factors, types of surgeries, CPB/aortic cross-clamping times (Tables 1, 2, 3, 4, 5) and hemodynamics (heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP) and central venous O_2 saturation) at all studied time intervals and left ventricular ejection fraction and Killip's classification of heart failure classes (at the time of LCOS and LV dysfunction diagnosis) and left ventricular ejection fraction (LVEF) (Tables 6, 7, 8, 9, 10).

The dose of consumed diuretics: mg/kg/h of frusemide (Table 11), (Figure 1) was comparable in both groups at diagnosis of LCOS and 24-h interval, but significantly less frusemide (21 mg/kg/h) was

Table 1. Comparison between Group A (control group) and Group B (study group) according to age and sex.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value*	*P*-value	Sig.
Age (yrs)	Mean ± SD	52.70 ± 9.78	52.27 ± 8.70	0.181•	0.857	NS
	Range	30–69	32–70			
Sex	Female	11 (36.7%)	11 (36.7%)	0.000•	1.000	NS
	Male	19 (63.3%)	19 (63.3%)			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
•: Independent t-test.
*.Chi-square test.The table shows that there was no statistically significant difference found between the two groups according to age and sex.

Table 2. Comparison between Group A (control group) and Group B (study group) according to height and weight.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value*	*P*-value	Sig.
Height (cm)	Mean ± SD	170.83 ± 9.04	169.37 ± 8.89	0.634	0.529	NS
	Range	156–187	157–186			
Weight (kg)	Mean ± SD	90.07 ± 12.80	84.53 ± 9.52	1.900	0.062	NS
	Range	77–120	58–97			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
*: Independent t-test. The table shows that no statistically significant difference was found between the two groups according to height and weight.

Table 3. Comparison between Group A (control group) and Group B (study group) according to risk factors.

		Group A (Control group)		Group B (Study group)				
		No.	%	No.	%	Test value*	*P*-value	Sig.
HTN	No	12	40.0%	12	40.0%	0.000	1.000	NS
	Yes	18	60.0%	18	60.0%			
DM	No	19	63.3%	22	73.3%	0.693	0.405	NS
	Yes	11	36.7%	8	26.7%			
Smoking	Non-smoker	17	56.7%	16	53.3%	0.067	0.795	NS
	Smoker	13	43.3%	14	46.7%			
Dyslipidemia	No	18	60.0%	18	60.0%	0.000	1.000	NS
	Yes	12	40.0%	12	40.0%			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
*: Chi-square test. The table shows no statistically significant difference was found between the two groups according to risk factors.

consumed in levosimendan group at 48-h interval as compared to beta-agonist group (26 mg/kg/h) to maintain adequate urine output (*P*-value 0.026).

Serum creatinine level (Table 12) was comparable between the two groups at the time of LCOS diagnosis and& at 24 -hours interval, while at 48 -hours interval, levosimendan group had significantly lower serum creatinine level (1.18 mg/dl) compared to beta-agonist group (1.53 mg/dl;) *P*-value 0.032).

At the time of ICU discharge, a highly significant difference was found between the two groups; levosimendan group had mean serum creatinine of 0.9 mg/dl compared to 1.27 mg/dl in beta-agonist group (*P*-value 0.001) (Figure 2).

About 30% of our patients (nine patients) in each group developed AKI (stage I as per definitions of "AKI classification" scale) at the time of diagnosis of low cardiac output state (LCOS); 44% out of these patients in beta-agonist (control) group progressed to renal failure (stage III) at the time of ICU discharge with overall incidence of renal failure in this group being 13.3% (four patients; *P*-value 0.038).

No statistically significant difference was found between the two groups according to creatinine level at the diagnosis of LCOS, AKI at diagnosis of LCOS and creatinine level at 24 h after diagnosis of LCOS (Figure 2).

4. Discussion

Post cardiac surgery LCOS is one of the most common and serious complications. LCOS was an independent predictor of longer hospital stay and ICU readmission and higher postoperative complications[12] and is one of the most common predisposing factors to AKI in the postoperative setting. With the incidence of post cardiac surgery acute kidney approaching 22–33%, perioperative cardioprotective and nephro-protective strategies should maintain organ perfusion and oxygen supply to tissues[13].

When inotropic support is not adequate to correct LCOS, intra-aortic balloon pump (IABP) counterpulsation and other ventricular-assist devices may be used.

Diuretics as well as renal replacement therapy are therapeutic options for AKI. However, none of the

Table 4. Comparison between Group A (control group) and Group B (study group) according to type of surgery.

	Group A (Control group)		Group B (Study group)				
	No.	%	No.	%	Test value*	*P*-value	Sig.
CABG on pump	12	40.0%	13	43.3%	0.069	0.793	NS
CABG off pump	1	3.3%	3	10.0%	1.071	0.301	NS
AVR surgery	2	6.7%	2	6.7%	0.000	1.000	NS
MVR surgery	4	13.3%	4	13.3%	0.000	1.000	NS
DVR surgery	6	20.0%	3	10.0%	1.176	0.278	NS
Combined valve and CABG	2	6.7%	3	10.0%	0.218	0.640	NS
Ascending thoracic aorta aneurysm surgery	3	10.0%	2	6.7%	0.218	0.640	NS

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
*: Chi-square test. The table shows that no statistically significant difference was found between the two groups according to the type of surgery.

Table 5. Comparison between Group A (control group) and Group B (study group) according to bypass and clamping time.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value•	*P*-value	Sig.
CPB time (min)	Mean ± SD	119.03 ± 25.56	109.89 ± 22.22	1.424	0.160	NS
	Range	85–170	85–160			
Clamping time (min)	Mean ± SD	81.90 ± 17.81	77.11 ± 17.08	1.025	0.310	NS
	Range	55–120	55–120			

Note: *P*-value >0.05: non significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS). The table shows that no statistically significant difference was found between the two groups according to bypass and clamping time.
•:Independent t-test.

Table 6. Comparison between Group A (control group) and Group B (study group) according to heart rate.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value•	*P*-value	Sig.
HR at diagnosis of LCOS (bpm)	Mean ± SD	115.63 ± 5.51	117.50 ± 6.48	−1.202	0.234	NS
	Range	103–128	107–133			
HR at 24 h of treatment (bpm)	Mean ± SD	113.70 ± 6.99	110.60 ± 6.91	1.728	0.089	NS
	Range	98–128	94–120			
HR at 48 h of treatment (bpm)	Mean ± SD	104.60 ± 7.03	101.57 ± 6.89	1.677	0.099	NS
	Range	91–120	92–113			
HR at the time of discharge (bpm)	Mean ± SD	91.10 ± 6.32	88.60 ± 4.19	1.806	0.076	NS
	Range	78–109	80–96			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value< 0.01: highly significant (HS). •:Independent t-test.
The table shows that no statistically significant difference was found between the two groups according to heart rate.

Table 7. Comparison between Group A (control group) and Group B (study group) according to mean arterial pressure.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value•	*P*-value	Sig.
MAP at diagnosis of LCOS (mmHg)	Mean ± SD	70.37 ± 4.36	72.13 ± 2.87	−1.853	0.069	NS
	Range	60–76	67–78			
MAP at 24 h of treatment (mmHg)	Mean ± SD	78.43 ± 5.16	76.83 ± 4.35	1.299	0.199	NS
	Range	71–93	69–86			
MAP at 48 h of treatment (mmHg)	Mean ± SD	83.40 ± 5.16	83.33 ± 3.90	0.056	0.955	NS
	Range	75–96	73–90			
MAP at the time of discharge (mmHg)	Mean ± SD	88.53 ± 5.72	88.73 ± 4.65	−0.149	0.882	NS
	Range	75–98	77–97			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS). MAP: mean arterial pressure.
•:Independent t-test.
The table shows that no statistically significant difference was found between the two groups according to MAP.

Table 8. Comparison between Group A (control group) and Group B (study group) according to CVP.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value•	*P*-value	Sig.
CVP at diagnosis of LCOS (cmH_2O)	Mean ± SD	18.77 ± 2.69	17.87 ± 2.50	1.343	0.185	NS
	Range	14–24	12–23			
CVP at 24 h of treatment (cmH_2O)	Mean ± SD	16.77 ± 2.53	15.57 ± 2.75	1.759	0.084	NS
	Range	12–22	8–19			
CVP at 48 h of treatment (cmH_2O)	Mean ± SD	13.23 ± 2.10	12.23 ± 2.61	1.637	0.107	NS
	Range	10–17	7–17			
CVP at thetime of discharge (cmH_2O)	Mean ± SD	10.37 ± 1.54	9.60 ± 1.75	1.798	0.077	NS
	Range	7–13	7–12			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value< 0.01: highly significant (HS). •:Independent t-test.
The table shows that no statistically significant difference was found between the two groups according to CVP.

Table 9. Comparison between Group A (control group) and Group B (study group) according to SVcO2.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value•	*P*-value	Sig.
$SvcO_2$ at diagnosis of LCOS (%)	Mean ± SD	49.70 ± 5.17	51.67 ± 3.72	−1.691	0.096	NS
	Range	34–58	44–58			
$SvcO_2$ at 24 h of treatment (%)	Mean ± SD	56.40 ± 5.45	58.13 ± 3.21	−1.501	0.139	NS
	Range	42–66	50–63			
$SvcO_2$ at 48 h of treatment (%)	Mean ± SD	62.30 ± 5.70	64.53 ± 4.19	−1.729	0.089	NS
	Range	50–72	55–70			
$SvcO_2$ at the time of discharge (%)	Mean ± SD	68.30 ± 5.25	69.73 ± 3.87	−1.204	0.233	NS
	Range	59–74	61–77			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS). •:Independent t-test.
The table shows that no statistically significant difference was found between the two groups according to $SvCO_2$.

Table 10. Comparison between Group A (control group) and Group B (study group) according to Killip Class and LVEF.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value	*P*-value	Sig.
Killip Class	Class II	19 (63.3%)	20 (66.7%)	0.359*	0.836	NS
	Class III	9 (30.0%)	9 (30.0%)			
	Class IV	2 (6.7%)	1 (3.3%)			
LVEF (%)	Mean ± SD	38.10 ± 3.08	36.40 ± 3.98	1.851•	0.069	NS
	Range	30–41	30–42			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
*: Chi-square test; •: Independent t-test. The table shows that no statistically significant difference was found between the two groups according to Killip Class and LVEF.

Table 11. Comparison between Group A (control group) and Group B (study group) according to diuretic dose.

		Group A (Control group)	Group B (Study group)			
		No. =	No. =	Test value*	*P*-value	Sig.
Diuretic dose at diagnosis of LCOS (mg/kg/h)	Mean ± SD	0.45 ± 0.07	0.44 ± 0.08	0.383	0.703	NS
	Range	0.32–0.55	0.22–0.57			
Diuretic dose at 24 h after diagnosis of LCOS (mg/kg/h)	Mean ± SD	0.39 ± 0.10	0.35 ± 0.10	1.640	0.106	NS
	Range	0.22–0.55	0.16–0.49			
Diuretic dose at 48 h after diagnosis of LCOS (mg/kg/h)	Mean ± SD	0.26 ± 0.08	0.21 ± 0.07	2.284	0.026	S
	Range	0.11–0.44	0.11–0.36			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
*: Chi-square test. The table shows that no statistically significant difference was found between the two groups according to diuretic dosage at diagnosis of LCOS and at 24 h after diagnosis of LCOS. Diuretic consumption was significantly low in levosimendan group at 48 h after LOCS diagnosis.

patients in our study required renal replacement therapy.

Levosimendan helps to protect the kidney in LCOS by two main effects. First, its inotropic effects improve cardiac output. Second is direct reno-vascular vasodilatory effect, as it is a potassium-ATP (K-ATP) channel opener with a vasodilator effect on renal artery with resultant improvement of renal perfusion. In addition, in a setting of renal hypoperfusion due to decreased cardiac output, levosimendan provides kidney protection by blocking mitochondrial K-ATP channels[14].

Table 12. Comparison between Group A (control group) and Group B (study group) according to serum creatinine level.

		Group A (Control group)	Group B (Study group)			
		No. = 30	No. = 30	Test value	*P*-value	Sig.
Creatinine level at diagnosis of LCOS (mg/dl)	Mean ± SD	1.33 ± 0.48	1.21 ± 0.48	1.008•	0.317	NS
	Range	0.7–2.6	0.54–2			
AKI at diagnosis of LCOS	No	21 (70.0%)	21 (70.0%)	0.000*	1.000	NS
	Yes	9 (30.0%)	9 (30.0%)			
Creatinine level at 24 h after diagnosis of LCOS (mg/dl)	Mean ± SD	1.55 ± 0.78	1.40 ± 0.70	0.785•	0.436	NS
	Range	0.7–4.1	0.6–3.3			
Creatinine level at 48 h after diagnosis of LCOS (mg/dl)	Mean ± SD	1.53 ± 0.72	1.18 ± 0.49	2.193•	0.032	S
	Range	0.6–3.1	0.53–2.7			
Creatinine level at time of ICU discharge (mg/dl)	Mean ± SD	1.27 ± 0.52	0.90 ± 0.19	3.637•	0.001	HS
	Range	0.6–2.5	0.55–1.3			
Renal failure at ICU discharge	No	26 (86.7%)	30 (100.0%)	4.286*	0.038	S
	Yes	4 (13.3%)	0 (0.0%)			

Note: *P*-value >0.05: non-significant (NS); *P*-value <0.05: significant (S); *P*-value <0.01: highly significant (HS).
*: Chi-square test. •: Independent t-test. The table shows that highly statistically significant difference was found between the two groups according to creatinine level at the time of discharge. Statistically significant difference was found between the two groups according to the creatinine level at 48 h after diagnosis of LCOS and incidence of renal failure at discharge.

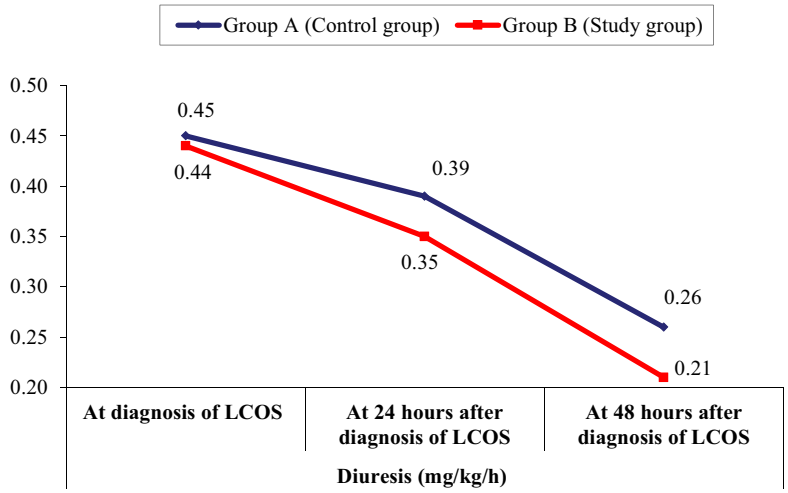


Figure 1. Comparison between Group A (control group) and Group B (study group) according to dose of diuretics used, showing that levosimendan group had significantly less dose of diuretics at 48-h interval from the time of diagnosis of LCOS compared to beta-agonist group, while diuretics consumption was comparable in both groups at the time of diagnosis of LCOS and 24 h later.

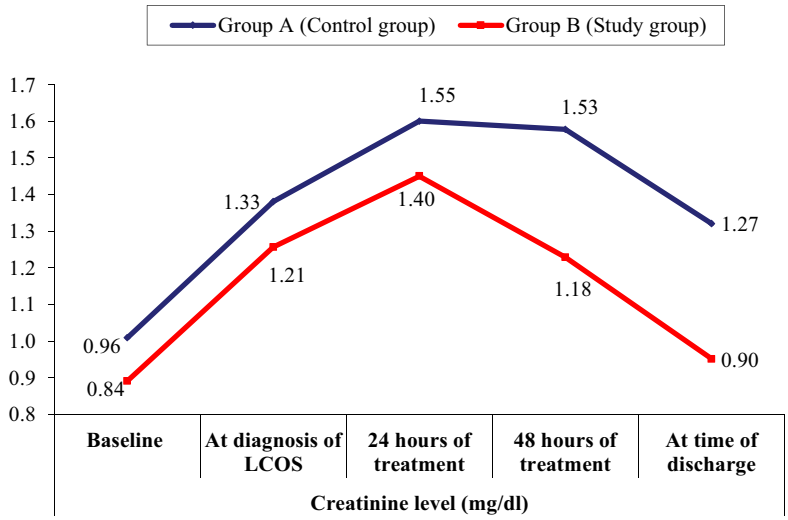


Figure 2. Comparison between Group A (control group) and Group B (study group) according to serum creatinine level showing that levosimendan group had significantly lower serum creatinine level at 48-h interval from the time of diagnosis of LCOS and a highly significant differences compared to beta-agonist group at the time of ICU discharge, while serum creatinine level was comparable in both groups at the time of diagnosis of LCOS and 24 h later.

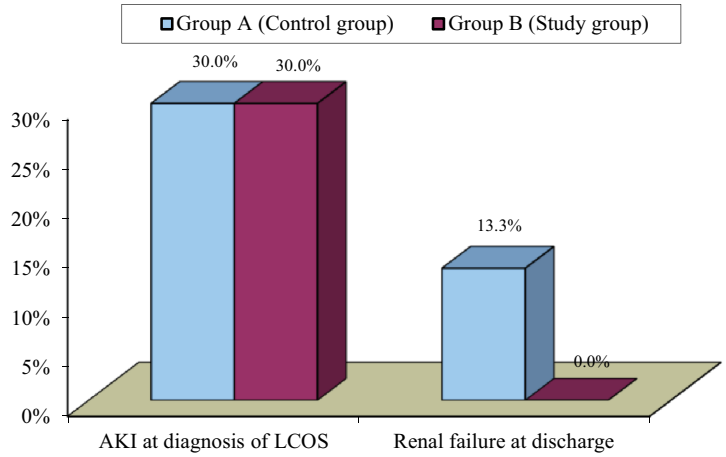


Figure 3. Bar chart comparing Group A (control group) to Group B (study group) according to the incidence of AKI at the time of diagnosis of LCOS and renal failure at the time of patient discharge from hospital. Thirty percent of patients in both groups developed AKI at the time of diagnosis of LCOS, while 13.3% of beta-agonist group discharged from ICU were with renal failure and none of levosimendan group were in renal failure state at the time of ICU discharge.

We hypothesized that levosimendan can provide a satisfactory reno-protective effects against kidney injury and failure in post cardiac surgery patients who developed left ventricular dysfunction and low cardiac output state owing to its cardiostimulatory as well as renal vasodilatory effects.

In our study, both groups (levosimendan and standard beta agonist groups) were similar regarding values of central venous oxygen saturation, HR, MAP and CVP. This finding supports the hypothesis that levosimendan has a protective effect on kidney function that is independent of its cardioprotective effect[15].

The dose of diuretics therapy at the time of diagnosis of LCOS and at 24-h interval was similar in both groups. However, levosimendan group significantly had less use of diuretics at 48-h interval from diagnosis of LCOS (Figure 1); this supports the better effect of levosimendan in maintaining urine output and renal protection over beta-agonists.

About 30% of our patients (nine patients) in each group developed AKI (stage I as per definitions of "AKI classification" scale) at the time of diagnosis of low cardiac output state (LCOS). And, 44% out of these patients in beta-agonist (control) group progressed to renal failure (stage III) at the time of ICU discharge with incidence of renal failure in this group being 13.3% (four patients) (Figure 2 and 3). All were managed conservatively with no patients requiring renal replacement therapy. In contrast, no patients in levosimendan (study) group developed renal failure.

These findings are in contrast to the findings of Guerrero et al.[9] that showed decreasing tendency of kidney injury with levosimendan at 24 h, and agree with their results at 48-h intervals of LCOS diagnosis.

The incidence of kidney injury developed at the time of diagnosis of post cardiac surgery LOCS in our study was similar to that reported by Guerrero and colleagues [9].

The reno-protective effect of levosimendan was also tested by Levin and colleagues [16] who conducted their study on more than 250 patients with severe left ventricular dysfunction who underwent coronary artery bypass graft surgeries. Preoperative levosimendan was tested against placebo with less incidence of postoperative kidney injury and failure with levosimendan.

Combining levosimendan with standard therapy of beta-blocker in patients with left ventricular dysfunction who underwent valve surgery in a study by Baysal and colleagues [17] showed better effects on renal function (serum creatinine level and glomerular filtration).

We did not test the relation of timing of initiation of levosimendan in low cardiac output state to its reno-protective efficacy post cardiac surgery, as we conducted our study on patients with normal left ventricular function and levosimendan was started once low cardiac output state was diagnosed. Yet, this is an area of controversy in literatures with many studies testing the time of initiation of levosimendan. One of these studies was conducted by Balzer and colleagues [18] who compared different timings of levosimendan initiation in patients with severe left ventricular dysfunction.

Also, Treskatsch and colleagues [19] compared early versus late levosimendan in patients with severe left ventricular dysfunction and/or low cardiac output states. They found that the incidence of acute kidney failure was significantly lower in patients who received early levosimendan therapy versus those who received late therapy.

On contrary to our results and other levosimendan-supporting studies Mehta and colleagues [20] objected

these results and reported no significant differences being found between levosimendan and placebo in patients with LVEF of 35% or less who underwent on-bypass cardiac surgery according to the need for renal replacement therapy at 30 days.

Also, Landoni and colleagues [21] found no significant differences between levosimendan and placebo in their multicenter study, which was conducted on patients who had perioperative cardiovascular dysfunction and required hemodynamic supports in terms of incidence of kidney failure as measured by the AKI scale or in the need for renal replacement therapy.

These different findings could be explained by different patient populations; both studies were conducted on patients with preoperative LV dysfunction and the need of hemodynamic support, different types of cardiac surgeries, the use versus nonuse of loading dose levosimendan and other different study settings.

In conclusion, levosimendan through its inotropic and nephroprotective effect may have a better role in the preservation of renal functions and in decreasing the incidence of kidney failure in patients with LCOS post cardiac surgery as compared to beta-agonists. Better renal protection in levosimendan group may be related to the added reno-protective effect, which is independent of its inotropic effect that counteracts the LCOS. This is suggested by the absence of significant hemodynamic differences between the two groups.

Further randomized, controlled trials with larger sample size and wide variability of patient characteristics and understanding the exact mechanism of renal and cardiac protection of levosimendan are needed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Index 1

Killip classification for heart failure (HF): Zafari 2019.

Class I	No clinical signs of heart failure
Class II	Findings consistent with mild-to-moderate heart failure (e.g. S3 gallop lung rales less than one-half way up the posterior lung fields or jugular venous distension)
Class III	Acute pulmonary edema
Class IV	Cardiogenic shock

Index 2

Acute kidney failure (AKI) score: Palevsky 2021.

	Serum creatinine (SCr) criteria	Urine output criteria
Stage 1	Increase ≥0.3 mg/dl within 48 h or increase ≥1.5 to 1.9 × reference SCr	<0.5 mL/kg/h for >6 consecutive hours
Stage 2	Increase ≥2 to 2.9 × reference SCr	<0.5 mL/kg/h for >12 h
Stage 3	Increase ≥3 × reference SCr or 1.5-fold increase to ≥4 mg/dl	<0.3 mL/kg/h for >24 h or anuria 12 h