Original Article

Levosimendan for patients with heart failure undergoing major oncological surgery: A randomised blinded pilot study

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ABSTRACT

Background and Aims: Cardiovascular diseases and cancer are among the leading causes of mortality worldwide. The aim of this study is to evaluate the efficacy and safety of preoperative administration of levosimendan in patients with chronic heart failure (CHF) scheduled for major abdominal oncologic surgery. **Methods:** This study included 60 patients with abdominal malignancy, ejection fraction (EF) <35% and CHF scheduled for surgery under isoflurane-fentanyl anaesthesia and were managed in the surgical intensive care unit perioperatively. They were randomised to receive levosimendan infusion ($n = 30$) at a dose of 0.1 μg/kg/min or placebo ($n = 30$) for 24 hours before surgery. **Results:** The risk of hypotension (RR: 0.40, 95% CI: 0.19-0.83) or decompensated heart failure (RR: 0.31, 95% CI: 0.12-0.76) was significantly lower in the levosimendan group. The ejection fraction, cardiac index and stroke volume index were significantly higher in the levosimendan group after surgery ($P < 0.001$). Duration of postoperative ventilation and hospital stay were significantly shorter in the levosimendan group ($P < 0.001$) while the frequency of dysrhythmia, deterioration of renal function and sepsis was comparable. **Conclusion:** In patients with low EF <35% and CHF, administration of levosimendan for 24 hours before major abdominal oncologic surgeries may reduce the risk of hypotension and decompensated heart failure and may improve cardiac function.

Key words: Heart failure, levosimendan, oncological surgery, perioperative

INTRODUCTION

Heart failure (HF) is an established risk factor for postoperative cardiac complications and death particularly in elderly undergoing non-cardiac surgeries.[1-3] Patients with HF who undergo major surgical procedures are at higher risks of operative mortality and hospital readmission than other patients, including those with coronary artery disease.[2,4] HF occurs in 1% to 6% of patients after major non-cardiac surgeries, the risk being higher, in patients with pre-existing cardiac conditions such as priorHF.[5,6]

Cardiac patients undergoing major abdominal oncologic surgeries which entails substantial fluid shift, blood loss and severe haemodynamic instability are at higher risk for perioperative HF.[3,7] Therefore, preoperative optimisation of such patients is of paramount importance through adequate cardiological assessment, optimisation of medications and ensuring normal volume status.[3,5] Besides, the prophylactic use of inotropic agents for preoperative optimisation of patients at high risk of HF remains controversial owing to their potential to jeopardise the myocardial oxygen supply-demand balance or to induce dysrhythmias with an assumed higher mortality.[3,8]

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Levosimendan is a calcium sensitiser drug with positive inotropic action that has been shown to safely improve cardiac performance and haemodynamics in HF patients without increasing the myocardial oxygen demand or causing dysrhythmias.[9-12] Calcium sensitisers are a new class of inotropic agents that enhance myocardial contractility through augmenting the sensitivity of the myofilaments to calcium, mainly by binding to troponin C. Among this group of sensitisers, levosimendan has got unique characteristics, as it increases the contraction force but does not impair ventricular relaxation.[12] Also, it selectively inhibits phosphodiesterase III and induces vasodilatation of systemic and coronary arterial resistance vessels. In contrast to other agents, levosimendan has got the advantage that the increased contractility is achieved without increasing myocardial oxygen consumption or inducing arrhythmias.[9-12] The perioperative use of levosimendan for optimisation of patients with HF has been reported in few studies with promising results regards to reduction of duration of postoperative ventilation, length of hospital stay and decreasing the incidence of postoperative HF and mortality, mainly for cardiac patients undergoing cardiac surgeries.[13-18] However, the literature search did not show relevant studies regarding its role in patients with chronic HF undergoing major cancer surgery.[15-18]

METHODS

This pilot randomised blinded trial was conducted at the Surgical Intensive Care Unit (SICU), Department of Anaesthesia and Intensive Care, National Cancer Institute, Cairo University, Cairo, Egypt from August 1st, 2017 to February 1st, 2018. Institutional Review Board (IRB) approval was obtained before study initiation (approval number 201617020.2P dated 18/07/2017) and all patients signed informed consents. The trial was also registered at ClinicalTrials.gov with an ID: NCT03557255. The full study protocol is available at the National Cancer Institute IRB, Cairo University, Cairo, Egypt.

Patients suffering from CHF with left ventricular ejection fraction <35% and scheduled for major abdominal oncologic surgery including total gastrectomy, hemicolectomy, total colectomy, abdomino-perineal repair and total pelvic exenteration with an expected blood loss >1000 ml, duration of surgery >4 hours and expected significant fluid shifts were eligible for inclusion in this study.

Exclusion criteria were restrictive or obstructive cardiomyopathy, severe cardiac valvular disease, history of atrial fibrillation, ventricular tachycardia or fibrillation, resting systolic arterial pressure <80 mmHg, second or third degree atrioventricular block, Child-Pugh class C liver cirrhosis, and severe renal failure (defined as creatinine clearance <30 ml/min). Patients with immediate postoperative complications such as surgical re-exploration for bleeding or suspected leak were not included.

The included patients were admitted to the SICU before the operation. Preoperative risk stratification was performed according to the Goldman Cardiac Risk Index,[6] New York Heart Association (NYHA), Revised cardiac risk index, and American Society of Anesthesiologists (ASA) classification. Transthoracic echocardiography was done upon recruitment. Patients were randomly allocated into one of two groups; Levosimendan group (n = 30) received levosimendan infusion and Control group (n = 30) received normal saline infusion for 24 hours before the scheduled time of surgery. A computer-generated random numbers list was used for the allocation of the participants. Block randomisation with a block size of 4 was used with 1:1 ratio of levosimendan and saline (control) groups. A master list of the interventions corresponding to each number was kept in a secure place by a third party (pharmacist) not directly connected with the study. Only at the end of the study the list was released to the investigators for the analysis of the results. The medications were prepared by the hospital pharmacy using identical infusion systems. Levosimendan was prepared in a concentration of 25 μg/ml and was infused at a rate of 0.1 μg/kg/minute without loading starting from 16 ml/kg for an average 70 kg patient. Indications for infusion rate reduction were the development of hypotension (SBP <80 mmHg), mean arterial pressure <65 mmHg in the absence of hypovolaemia or premature beats in a frequency exceeding 6/min or occurrence of a significant arrhythmia occurring in runs. If such occurrences persisted despite infusion rate reduction, infused medication would be discontinued. All this monitoring was done in the SICU pre-operatively. In the control group, an identical saline infusion regimen was employed. In both groups, the infusion was stopped prior to surgery and was not continued during surgery.

All patients were monitored using continuous electrocardiography (ECG) and pulse oximetry. Arterial blood pressure (ABP) was monitored invasively via

an indwelling arterial catheter inserted into the left radial artery (or the right for left-handed persons). Urine output was monitored via an indwelling urinary catheter. Patients were operated upon after 24-hour management in the SICU. Echocardiography was repeated immediately before surgery.

All patients were monitored intra-operatively with ECG, capnography, pulse oximetry, nasopharyngeal temperature and invasive ABP. Anaesthesia was induced using intravenous (IV) fentanyl 2 μg/kg and propofol 1.5 mg/kg. Tracheal intubation was facilitated with IV cisatracurium 1 mg/kg. Ventilation was controlled using a preset tidal volume of 7 to 10 ml/kg with adjustment of the respiratory rate to maintain an end-tidal CO_2 of 30 to 40 mmHg. Anaesthesia was maintained using isoflurane in 60% oxygen/40% air. The concentration of isoflurane was adjusted to keep the BIS between 40 and 60. Supplemental doses of IV cisatracurium were given at a dose of 0.05 mg/kg to keep the train of four (TOF) count at 2 or less. After induction of anaesthesia, a pulmonary artery catheter was inserted via the right internal jugular vein to monitor the cardiac filling pressures, cardiac index (CI) and stroke volume index (SVI). Fluid management was guided by the cardiac filling pressure and packed red blood cells were transfused to keep the haematocrit above 30%.

At the end of the procedure, Isoflurane was discontinued, and the trachea was kept intubated and the patient sedated with an IV infusion of fentanyl 1 μg/kg/h and were transferred to the SICU. At the SICU, volume-controlled synchronised intermittent mechanical ventilation (VC-SIMV) was maintained until the patients fulfilled the criteria for weaning that was carried out according to a standard institutional protocol when the patients were fully conscious, able to take tidal volume of 5-7 ml/kg with respiratory rate less than 20/min. Following extubation, patient-controlled analgesia (PCA) using intravenous fentanyl was provided to control postoperative pain. Invasive haemodynamic monitoring was continued for at least 24 hours after which the patients were discharged to a step-down unit. Criteria for transfer were a fully conscious, haemodynamically stable patient on no inotropic or vasopressor infusion and with no metabolic, electrolyte or acid-base abnormality. Non-invasive haemodynamic monitoring continued at the step-down unit using ECG, non-invasive arterial pressure, pulse oximetry and urine output until patients were eligible for hospital discharge. Patients were discharged from the hospital when they were able to ambulate, resumed oral intake, could void unaided, regained normal bowel functions and had no surgical complication. Transthoracic echocardiography was repeated on the 7th postoperative day. The cardiologist who performed the echocardiography was blinded to the study groups and the previous echo results of all patients.

The primary outcome measure was development of postoperative complications; namely, hypotension and decompensated HF, difficult weaning from mechanical ventilation (if failed after 16 hours of postoperative ventilation according to the local institutional protocol, rapid shallow breathing index >150 and PaO2/FiO2 ratio <150) and length of hospital stay. The secondary outcome measures were EF, CI, SVI, and duration of postoperative ventilation. Decompensated HF was defined as development of acute pulmonary oedema or hypotension with mean ABP ≤65 mmHg. Deterioration of renal function diagnosed if serum creatinine was increased by ≥0.3 mg/dL within 48 hours, urine volume <0.5 mL/kg/hour for six hours and increase in serum creatinine to ≥1.5 times baseline from preoperative values according to acute kidney injury (AKI) criteria of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Patients and caregivers involved in patient management, assessment of the outcome measures and data analysis were blinded to the intervention received.

The required sample size was calculated using the G*Power© Software version 3.1.3 (Universität Düsseldorf, Germany). There were no previous trials comparing the two studied groups of the current trial. We expected a small standardised effect size of 0.2 from the primary outcome. Based on this effect size, 30 subjects will be needed to elicit the difference between the two groups at an alpha level of 0.05 and power of 0.9 according to the recommendation of Whitehead *et al*. (2016). Statistical analysis was done using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Continuous variables were presented as mean (standard deviation) and inter-group differences were compared using the unpaired *t*-test. Two-way mixed ANOVA was used to test for interaction between treatment and time. Simple main effects using *t*-test was reported whenever significant interaction is observed. Categorical variables were presented as ratio or number and percentage and between-group differences were compared using Fisher's exact test. Risk for adverse

outcomes was estiamted as a relative risk (RR) with its 95% confidence interval (CI). Two-tailed *P* values <0.05 are considered statistically significant.

RESULTS

Ninety-six patients were assessed for eligibility, of which 31 patients were primarily excluded because of refusal to participate in the study (n = 9) or failure to meet the eligibility criteria (n = 22). Sixty-five patients were recruited and were randomised to receive levosimendan (n = 32) or placebo (n = 33). Five patients were secondarily excluded [Figure 1]. The characteristics of patients and the operative details are shown in Table 1. Both groups were comparable with regard to demographic characteristics and operative details. The preoperative levosimendan infusion was not discontinued because of adverse outcomes in any of the patients [Table 2]. The duration of postoperative ventilation and hospital stay were significantly shorter in the levosimendan group (P = 0.020 and P = 0.004, respectively). In control group 18 (60%) patients and in levosimendan group 9 (30%) patients couldn't be extubated before 7 pm as they did not meet extubation criteria (P value = 0.02).

The risk for hypotension (RR = 0.40, 95% CI = 0.19 to 0.83, P = 0.003) and hypotension requiring vasopressor administration (RR = 0.50, 95% CI = 0.24 to 1.02, P = 0.028) were significantly lower in the levosimendan group. Only 4 patients (13%) in the levosimendan group developed decompensated HF after surgery 'dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea (PND), peripheral edema, nausea/vomiting, elevated jugular venous pressure, pulmonary rales, cardiac gallops (S3 or S4)', as compared with 16 (53%) patients in the control group (RR = 0.31, 95% CI = 0.12 to 0.76, P = 0.001). The proportion of patients who developed postoperative dysrhythmias, deterioration of renal function, sepsis or difficult weaning from mechanical ventilation was comparable in both groups (P = 0.129, 0.424, 0.542 and 0.067, respectively).

The perioperative changes in the EF, CI and SVI are shown in Table 3 and Figures 2-4. A significant interaction between treatment and time was recognised in EF, CI, and SVI (P < 0.001 for all comparisons). Descriptive statistics showed that levosimendan treatment increased EF, CI and SVI, whereas the saline group showed decrease in those parameters. Simple main effects analysis showed that the two groups had comparable EF 24 hours before surgery, and comparable CI and SVI immediately after induction of anaesthesia. Immediately before surgery and seven days post-surgery, EF was significantly higher in the Levosimendan group (P < 0.001). CI and

Table 1: Baseline characteristics of the two studied groups

Variable	Levosimendan (n=30)	Control (n=30)	*P*
Age (years)	61.7 (3.2)	60.2 (2.9)	0.062
Gender (M/F)	18/12	22/8	0.273
ASA III/ASA IV	22/8	20/10	0.573
NYHA II/NYHA III	26/4	26/4	1.000
EF on recruitment (%)	28.0 (4.0)	27.0 (5.0)	0.396
Associated medical diseases			
Hypertension	26 (87%)	22 (73%)	0.197
Diabetes	18 (60%)	20 (67%)	0.592
Regular medications			
Beta blockers	28 (93%)	26 (87%)	0.671
ACE inhibitors	14 (47%)	10 (33%)	0.292
ARBs	10 (33%)	16 (53%)	0.118
Digitalis	8 (27%)	12 (40%)	0.273
Amiodarone	0 (0%)	2 (7%)	1.000
Hydralazine	4 (13%)	10 (33%)	0.067
Diuretics	10 (33%)	14 (47%)	0.292
Statins	22 (73%)	24 (80%)	0.542
Surgical procedure			0.448
Total gastrectomy	6 (20%)	8 (27%)	
Right hemicolectomy	4 (13%)	4 (13%)	
Total colectomy	6 (20%)	2 (7%)	
Abdomino-perineal repair	10 (33%)	8 (27%)	
Total pelvic exenteration	4 (13%)	8 (27%)	
Operative time (min)	221 (37)	232 (29)	0.205
Duration of postoperative ventilation (h)	16.5 (2.3)	19.2 (2.5)	<0.001
Duration of Hospital stay (days)	8.5 (2.3)	12.6 (4.5)	<0.001

Data are presented as mean (standard deviation), ratio or number (percentage)

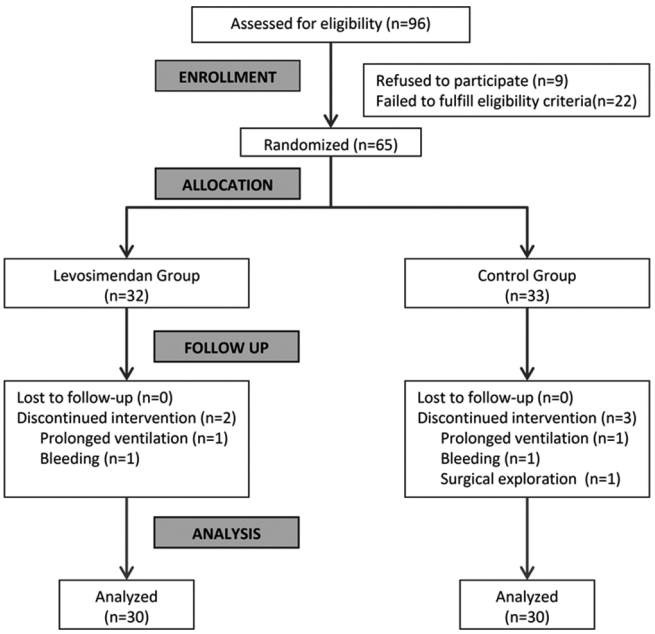

Figure 1: Flowchart showing the study progress

Table 2: Postoperative complications and adverse outcomes in the two studied groups

Adverse outcome	Levosimendan (*n*=30)	Control (*n*=30)	*P*	RR	95% CI
Hypotension	6 (20%)	17 (57%)	0.003	0.40	0.19 to 0.83
Hypotension requiring vasopressor	6 (20%)	14 (47%)	0.028	0.50	0.24 to 1.02
Decompensated heart failure	4 (13%)	16 (53%)	0.001	0.31	0.12 to 0.76
Dysrhythmia	2 (7%)	6 (20%)	0.129	0.46	0.14 to 1.58
Deterioration of renal function	2 (7%)	5 (17%)	0.424	0.54	0.16 to 1.79
Sepsis	6 (20%)	8 (27%)	0.542	0.82	0.42 to 1.60
Difficult weaning from MV	4 (13%)	10 (33%)	0.067	0.51	1.03 to 2.62

Data are presented as number (percentage). MV – Mechanical ventilation; RR – Relative risk; CI – Confidence interval

Table 3: Perioperative changes in the ejection fraction, cardiac index and stroke volume index in the two studied groups

	Levosimendan (*n*=30)	Control (*n*=30)	*P*
EF (%)			
24 h before surgery	29.6 (2.9)	29.9 (2.7)	0.680
Immediately before surgery	35.8 (3.6)	30.0 (2.8)	<0.001
7 days after surgery	39.6 (3.7)	28.1 (2.3)	<0.001
CI (l/min/m^2)			
Immediately after induction	3.1 (0.3)	3.1 (0.3)	0.604
Immediately after surgery	3.2 (0.3)	2.9 (0.3)	<0.001
24 h after surgery	3.3 (0.3)	2.9 (0.2)	<0.001
SVI (ml/m^2)			
Immediately after induction	40.8 (4.1)	39.4 (2.5)	0.110
Immediately after surgery	44.1 (4.0)	34.1 (2.1)	<0.001
24 h after surgery	46.3 (4.4)	35.2 (2.3)	<0.001

Data are presented as mean (standard deviation). EF – Ejection fraction; CI – Cardiac index; SVI – Stroke volume index

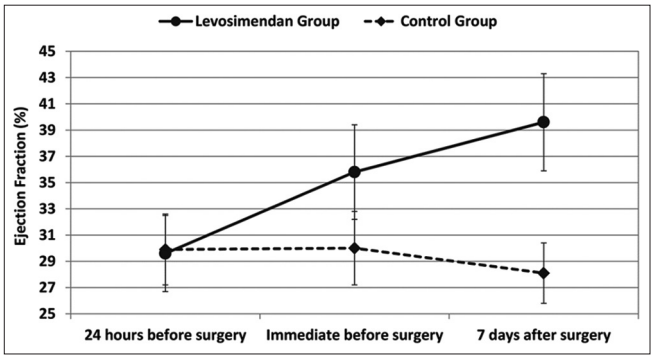

Figure 2: Mean ejection fraction in both study groups. Error bars represent the standard deviation

SVI were significantly higher in Levosimendan group immediately after surgery and 24 hours after surgery ($P < 0.001$).

DISCUSSION

Cancer patients with pre-existing cardiac disease or those receiving chemotherapy and scheduled for non-cardiac major surgeries may be at higher risk of postoperative cardiac complications.[2,4,19,20] Of particular concern is the risk imposed by CHF as an independent risk factor for perioperative cardiac events[21] and mortality.[2,21]

The prophylactic use of positive inotropic drugs for the perioperative management of CHF remains controversial.[3,8,22] In a randomised trial, dobutamine, not only failed to improve outcomes but was associated with increased morbidity and mortality,[8] possibly due to its unfavourable effect on myocardial oxygen supply-demand balance.[6] In contrast, another study reported that optimisation of haemodynamic parameters with pharmacological agents, including inotropes and judicious use of intravenous fluids and blood products could reduce postoperative cardiovascular morbidity and mortality in patients undergoing major elective non-cardiac, non-thoracic surgical procedures.[22]

The use of levosimendan for perioperative optimisation of patients with CHF undergoing cardiac surgery has been reported in some recent studies with promising results regarding its safety and efficacy.[13-17,23-25] In general, it is advisable to start levosimendan treatment 24 hours before surgery. However, one trial reported that levosimendan infusion for as short as 2 hours before surgery resulted in a significant increase in CI and SVI with significant reduction in systemic vascular resistance index (SVRI) in elderly HF patients undergoing emergency hip fracture repair.[26] To the authors' knowledge, very limited previous trials had evaluated the role of levosimendan for the perioperative optimisation of patients with CHF undergoing non-cardiac surgery, while most of the recent studies are focusing on its effects on cardiac patients undergoing cardiac surgeries.[23-25]

This study demonstrated that preoperative levosimendan administration significantly decreased the overall risk of perioperative hypotension and decompensated HF after elective abdominal oncologic surgery in patients with CHF and EF <35%. It resulted in a significant improvement in EF, CI and SVI as compared with patients receiving placebo for 24 hours

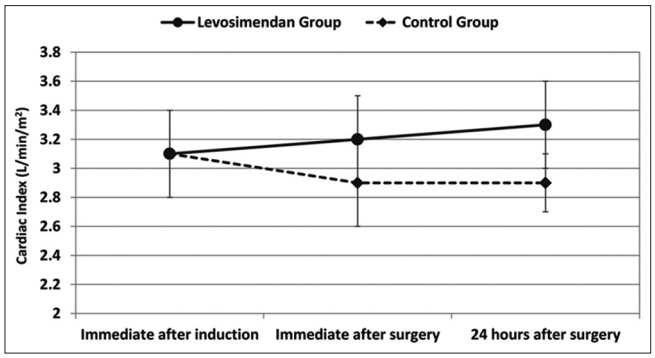

Figure 3: Mean cardiac index in both study groups. Error bars represent the standard deviation

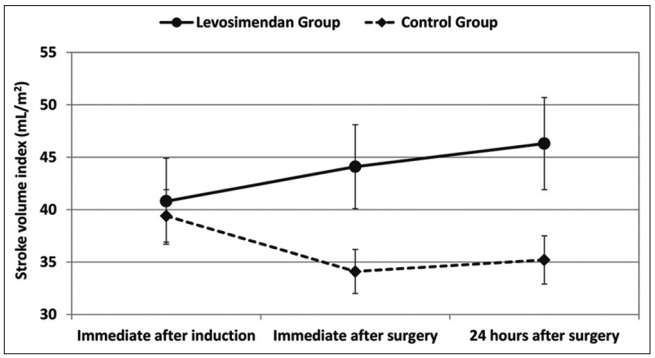

Figure 4: Mean stroke volume index in both study groups. Error bars represent the standard deviation

preoperatively and these effects were sustained for 7 days postoperatively. These favourable effects can be due to positive inotropic action of levosimendan that has been shown to safely improve cardiac performance and haemodynamics in HF patients without increasing the myocardial oxygen demands or causing dysrhythmias. In addition, levosimendan infusion was neither accompanied by any significant changes in the heart rate, systemic blood pressure, cardiac filling pressures nor discontinued because of any of these side effects in any patient.

The authors didn't have a clear explanation for the insignificant difference between both groups regarding the CI and SVI immediately after induction. It was assumed that these changes may be due to 2 reasons: First: since EF = SV/End diastolic volume (EDV), hence another factor EDV (not measured in this study) affects the EF. Levosimendan may have affected EDV (i.e. optimizing the preload) hence the early –before induction – statistically significant improvement in EF between both groups. Secondly, in the placebo group; CI and SVI were affected by anaesthetics, fluid shift and blood loss (all are affecting the cardiac pump function negatively) while in the levosimendan group patients were protected by the drug, hence the evident significant difference between both groups in CI and SVI by the end of surgery.

In the current study, levosimendan also decreased significantly the duration of postoperative ventilation and the total hospital stay which was consistent with other studies.[24-26] In addition, the incidence of decompensated HF was significantly decreased which was similar to the study done by Katsaragakis *et al*.[15]

Interestingly, the active metabolite of levosimendan has a long half-life (70-80 hrs) and has been detected in the circulation up to 2 weeks after discontinuation of a 24-hour infusion.[27,28] Such effects on cardiac performance are sustained for at least 7 days after discontinuation of the medication[11,29,30] as demonstrated in the present study.

A major limitation in the present study is the limited sample size. There were limited available previous considerable trials regarding the use of levosimendan for non-cardiac surgeries. However, the study is primarily presented as a randomised pilot trial to assess the efficacy and feasibility of using levosimendan to optimise CHF patients undergoing abdominal oncological procedures; an indication that has not been adequately studied previously. The present trial offers results that may serve for hypothesis testing in a larger RCT that is adequately powered to evaluate both the efficacy and safety of using levosimendan in this setting.

CONCLUSION

In conclusion, preoperative administration of levosimendan for 24 hours to patients with history of CHF prior to elective abdominal oncologic surgery may limit postoperative cardiac complications and may improve cardiac performance. These results are preliminary and larger randomised controlled trials are needed to determine the safety of levosimendan in this context and to identify the optimal timing, dosage and duration of infusion of the medication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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