PERIOPERATIVE USE OF LEVOSIMENDAN IN PATIENTS WITH IMPAIRED RIGHT VENTRICULAR FUNCTION UNDERGOING CARDIAC SURGERY WITH CARDIOPULMONARY BYPASS: A RANDOMIZED CONTROLLED STUDY

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Received: 13/10/2023
Accepted: 18/11/2023

Online ISSN: 2735-3540

ABSTRACT:

Background: *The purpose of this study is to investigate the impact of levosimendan on right ventricular (RV) function in patients with reduced RV function after open heart surgery with cardiopulmonary bypass (CBP).*

Aim of The Work: *The purpose of this study was to investigate the impact of levosimendan on RV function in patients who already had reduced RV function after open heart surgery with CBP.*

Patients and Methods: *The study included 120 adult patients submitted to cardiac surgery. All patients had impaired right ventricular function. In the levosimendan group (n=60), patients were admitted to ICU preoperatively and levosimendan infusion started after insertion of an arterial line 12 hours before surgery and was continued in operating room and then in the ICU (total infusion time of 24 hours). In the standard treatment group, patients (n=60) were managed with standard care according to our institutional protocol.*

Results: *Intraoperatively, patients in the levosimendan group had significantly higher TAPSE as compared to the control group (13.7 ± 0.99 versus 11.9 ± 1.3 mm, p<0.001). The advantage of levosimendan group continued at postoperative days 1, 3 and 7. In addition, it was shown that patients in the levosimendan group had significantly lower vasoactive inotrope score (VIS) at 12, 24 and 48 hours when compared to control groups. Furthermore, levosimendan group experienced significantly lower rate of rapid AF, shorter MV duration, shorter ICU and hospital stay.*

Conclusion*: Prophylactic use of levosimendan improves RV function and overall outcomes in patients undergoing open-heart surgery.*

Keywords: *Right ventricular Dysfunction; Levosimendan; Cardiac surgery.*

INTRODUCTION:

Perioperative right ventricular (RV) dysfunction after cardiac surgery with cardiopulmonary bypass (CBP) is associated with increased need for inotropic support, longer ICU stay, increased hospital readmission, and in-hospital mortality [(1-5)]. Suggested risk factors include deficient myocardial protection during surgery, CPB) time > 150 minutes, coronary embolism and acute graft occlusions. Also, reduced postoperative perfusion may lower RV contractility, especially if the right coronary artery is stenotic. Among the multiple echocardiographic approaches used for assessment of RV function, the most used parameter is tricuspid annular plane systolic excursion (TAPSE), measured using M-mode in an apical four chamber view [(6&7)].

To improve post-CPB RV performance, inotropic drugs are typically started during the perioperative phase. However, inotropes,

carry the danger of increased myocardial oxygen consumption, which can lead to cardiac ischemia and damage to hibernating but viable myocardium, as well as arrhythmias [8-10].

The therapeutic efficacy of levosimendan has been demonstrated in various studies. Its favorable pharmacokinetics and effects on ventricular function are widely known. It's characterized by three-pronged mode of action and long duration of action (up to 7-9 days) which is mainly attributed to its active metabolite (approximately 80 hours half-life) [11&12].

The interaction of levosimendan with cardiac troponin C, which forms the basis of its Ca2+-sensitizing mechanism [13]. Binding to troponin C makes troponin C fibers more sensitive to ionic free calcium, which helps prolong the molecular interaction between troponin C and troponin I, enhancing cardiac contractility without increasing ionic free calcium. This distinguishes levosimendan from all other inotropic drugs [14&15].

In addition, levosimendan has vasodilatory properties. It opens ATP-dependent potassium channels in vascular smooth muscles to induce dilation of coronary, peripheral, and pulmonary arteries as well as vasodilation of the portal and saphenous systems, resulting in a reduction in right ventricular preload and afterload [16]. Moreover, levosimendan ability to open cardiac mitochondrial ATP-sensitive K+ channels has been shown to diminish the formation of free radicals within cells. This, in turn, protects cells from stressful situations and inhibits cell [17&18].

AIM OF THE WORK:

The purpose of this study was to investigate the impact of levosimendan on RV function in patients who already had reduced RV function after open heart surgery with CBP.

PATIENTS AND METHODS:

The study included 120 adult patients submitted to cardiac surgery. All patients had impaired right ventricular function with TAPSE ≤15 mm as measured at any time within 30 days before surgery. Exclusion criteria included restrictive or obstructive cardiomyopathy, constrictive pericarditis, restrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent on venous return. Patients with evidence of systemic bacterial, systemic fungal, or viral infection within 72 h before surgery, chronic dialysis, estimated creatinine clearance ≤30 mL/min, weight ≥150 kg, systolic blood pressure (SBP) not managed to ensure SBP ≥ 90 mmHg at initiation of study drug, heart rate ≥120 beats/min, persistent for at least 10 min at screening and unresponsive to treatment, hemoglobin ≤ 8 g/dL, liver dysfunction with Child Pugh class B or C or severely compromised immune function were also excluded from the study. Eligible patients were equally and randomly assigned to one of the two treatment groups using computer generated allocation tables and sealed envelope technique.

Detailed baseline data including demographics, comorbidities, diagnosis, preoperative TAPSE and right ventricular systolic pressure (RVSP) were collected. CBP time and aortic cross clamping time were recorded. In the levosimendan group (n=60), patients were admitted to ICU preoperatively and levosimendan infusion started after insertion of an arterial line 12 hours before surgery in the ICU at a dose of 0.2 μg kg/min for the first hour and then reduced to 0.1 μg kg/ min and was continued in operating room and then in the ICU (total infusion time of 24 hours). In the standard treatment group, patients (n=60) were managed with standard care according to our institutional protocol.

Anesthesia and CPB management were standardized for all patients. Patients were transferred to adult post-surgical ICU after surgery, intubated on mechanical ventilation and managed according to our institutional protocols.

Outcome measures in the present study included right ventricular function assessed by measuring TAPSE in millimeters by trans-esophageal echocardiography (TEE) intraoperatively and on days 1,3 and 7 postoperatively and right ventricular systolic pressure (RVSP) measured in mmHg by TEE intraoperatively and on days 1, 3 and 7 postoperatively.

Other outcome measures were hours of mechanical ventilation, vasoactive inotrope score (VIS) at admission, 12 hours, 24 hours, and 48 hours, ICU stay, hospital stay and development of arrhythmia.

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, unpaired student t-test was used to compare between two groups in quantitative data, chi-square test was used to compare between groups in qualitative data and paired Student T-test was used to compare between related sample by (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). p value <0.05 was considered statistically significant.

Ethical consideration:

The present randomized controlled study was approved by the local ethical committee (FMASUR139/2021 on 18/02/2021) in line the 1964 Helsinki Declaration and its subsequent revisions. The study was registered at clinicaltrials.gov (NCT05063370). Written informed consent was obtained from all participants or their legal guardians.

RESULTS:

The present randomized controlled study included 60 patients in the levosimendan group and 60 patients in the control group. Comparison between the studied groups regarding the preoperative and operative characteristics revealed no statistically significant differences. Table (1).

Table 1: Preoperative and operative characteristics in the studied groups

	Levosimendan group N=60	Control group N=60	p value
Age (years) mean ± SD	49.6 ± 8.9	49.7 ± 10.3	0.99
Male/female n	42/18	39/21	0.56
Weight (Kg) mean ± SD	74.0 ± 12.9	71.9 ± 16.8	0.67
Comorbidities n (%)			
DM	9 (15.0)	14 (23.3)	0.25
Hypertension	9 (15.0)	12 (20.0)	0.47
RHD	51 (85.0)	49 (81.7)	0.62
AF	38 (63.3)	31 (51.7)	0.2
IHD	4 (6.7)	2 (3.3)	0.4
Type of surgery n (%)			
Mitral valve replacement	43 (71.7)	50 (83.3)	0.13
Tricuspid valve replacement	27 (45.0)	31 (51.7)	0.47
Aortic valve replacement	11 (18.3)	10 (16.7)	0.81
redo mitral valve replacement	10 (16.7)	5 (8.3)	0.17
CABG	4 (6.7)	2 (3.3)	0.4
VSD repair	3 (5.0)	-	0.08
CPB time (min.) mean ± SD	106.3 ± 31.7	97.8 ± 20.5	0.32
Aortic cross clamp time (min.) mean ± SD	65.2 ± 25.4	55.3 ± 15.4	0.14

AF: Atrial fibrillation, CABG: Coronary artery bypass grafting, CPB: Cardiopulmonary bypass, DM: Diabetes mellitus, IHD: Ischemic heart disease, RHD: Rheumatic heart disease, VSD: Ventricular septal defect.

Preoperatively, no significant differences were found between the studied groups regarding TAPSE (13.4 ± 1.0 versus 13.1 ± 1.1 mm, p=0.38). Intraoperatively, patients in the levosimendan group had significantly higher TAPSE as compared to

the control group (13.7 ± 0.99 versus 11.9 ± 1.3 mm, p<0.001). The advantage of levosimendan group continued at postoperative days 1 (14.7 ± 1.0 versus 11.3 ± 0.9 mm, p<0.001), 3 (15.1 ± 0. 9 versus 11.5 ± 0.9 mm, p<0.001) and 7 (15.2 ± 0.8 versus 11.7 ± 0.8 mm, p<0.001). Table (2).

Table 2: Right ventricular functions in the studied groups

	Levosimendan group N=60	Control group N=60	p value
TAPSE mm mean ± SD			
Preoperative	13.4 ± 1.0	13.1 ± 1.1	0.38
Intraoperative	13.7 ± 0.99	11.9 ± 1.3*	<0.001
Postoperative day 1	14.7 ± 1.0*	11.3 ± 0.9*	<0.001
Postoperative day 3	15.1 ± 0. 9*	11.5 ± 0.9*	<0.001
Postoperative day 7	15.2 ± 0.8*	11.7 ± 0.8*	<0.001
RVSP mmHg mean ± SD			
Preoperative	62.6 ± 18.1	57.8 ± 17.1	0.39
Intraoperative	59.0 ± 17.2*	50.2 ± 11.1*	0.062
Postoperative day 1	49.4 ± 9.8*	45.4 ± 9.2*	0.19
Postoperative day 3	46.3 ± 6.7*	45.2 ± 9.2*	0.7
Postoperative day 7	44.0 ± 6.6*	44.6 ± 8.5*	0.81

RVSP: Right ventricular systolic pressure, TAPSE: Tricuspid annular plane systolic excursion
* Significant results versus preoperative data

In the levosimendan group, TAPSE significantly increased at the postoperative days 1,3 and 7 as compared to the pre-operative values while in the control group, TAPSE significantly declined intraoperatively and at the postoperative days 1,3 and 7 as compared to the preoperative values Table (2).

In both groups, RVSP significantly decreased intraoperatively and at the postoperative days 1,3 and 7 with no statistically significant differences between groups at different follow up stations Table(2).

In addition, it was shown that patients in the levosimendan group had significantly lower VIS at 12 (3.6 ± 3.8 versus 13.3 ± 5.7, p<0.001), 24 (1.0 ± 1.9 versus 9.5 ± 5.7, p<0.001) and 48 (0.0 ± 0.0 versus 4.6 ± 5.9, p<0.001) hours when compared to control groups Table (3).

Table 3: Other outcome parameters in the studied groups

	Levosimendan group N=60	Control group N=60	p value
VIS mean ± SD			
Admission	10.3 ± 4.8	13.6 ± 6.9	0.29
12 hours	3.6 ± 3.8*	11.3 ± 5.7*	<0.001
24 hours	1.0 ± 1.9*	9.5 ± 5.7*	<0.001
48 hours	0.0 ± 0.0*	4.6 ± 5.9*	<0.001
Rapid AF n (%)	2 (3.3)	15 (25.0)	0.001
MV duration (hours) mean ± SD	7.8 ± 1.6	14.8 ± 6.1	<0.001
ICU stay (days) mean ± SD	2.3 ± 0.6	3.6 ± 1.1	<0.001
Hospital stay (days) mean ± SD	5.3 ± 1.1	8.3 ± 2.0	<0.001

AF: Atrial fibrillation, ICU: Intensive care unit, MV: Mechanical ventilation, VIS: Vasoactive inotrope score
* Significant results versus preoperative data

Furthermore, levosimendan group experienced significantly lower rate of rapid AF (3.3 % versus 25.0 %, p=0.001), shorter MV duration (7.8 ± 1.6 versus 14.8 ± 6.1

hours, p<0.001), shorter ICU stay (2.3 ± 0.6 versus 3.6 ± 1.1 days, p<0.001) and shorter hospital stay (5.3 ± 1.1 versus 8.3 ± 2.0 days, p<0.001). Table (3).

DISCUSSION:

In the present study, use of levosimendan was linked to improved RV function in patients submitted to cardiac surgery with CPB. Our findings are supports by the conclusions of other studies including variable populations.

Yaoshi et al., [19] meta-analysis found that levosimendan administration significantly raised TAPSE in patients with heart dysfunction. Likewise, Chao Qu et al., [20] noted that in patients with acute decompensated right heart failure, use of levosimendan improved in the TAPSE.

In this study, patients in both groups experienced significantly lowered intra-operative and postoperative RVSP in comparison to the postoperative values. The role of levosimendan in reducing RVSP was also documented by the study of Parissis et al., [21], who observed a decrease in RVSP with levosimendan use in their study on effects of levosimendan on right ventricular function in patients with advanced heart failure. Also, Hansen et al., [22] in their study on levosimendan use in right ventricular failure as they found that levosimendan was able to reduce RV afterload and RVSP.

In addition, our study noted that the use of levosimendan was related to a lower VIS score. This is supported by Orriach et al., [23] and Sheng et al., [24] findings who reported reduced dosage and duration of catecho-lamine infusion with levosimendan use.

In our work, levosimendan administration was associated shorter duration of MV and ICU and hospital stays. This agrees with the results of Luo et al., [25] who found that levosimendan effectively improved weaning rates from MV. Also, Triapepe and co-authors [26] showed a significant reduction in the length of ICU stay and tracheal intubation time with levosimendan use. However, Anastasiadis et al., [27] noted that levosimendan had no influence on lengths of ICU and total in-hospital stays in their study on the effectiveness of prophylactic levosimendan in patients undergoing CABG. Lomivorotov et al. [28] also investigated the benefits of levosimendan on 90 patients with coronary artery disease. Patients in the levosimendan group had significantly shorter ICU stays compared to other groups.

Finally, our study found that lower prevalence of perioperative arrhythmia in the levosimendan group in accordance with Sheng et al., [24] who concluded that the incidence of new AF was considerably lower in the levosimendan group than in the control group. In contrast, Mehta and coauthors [29] found that the rates of, atrial fibrillation, ventricular tachycardia, or fibrillation, resuscitated cardiac arrest, did not differ significantly between the levosimendan group and the placebo group.

In conclusion, our findings suggest that prophylactic use of levosimendan improves right ventricular function and overall outcomes in patients with impaired right ventricular function undergoing open-heart surgery.

Data Availability Statement

Data of this research will be available upon reasonable request.

Competing interests

Authors state no conflict of interest.

Funding

The research is self-funded from the authors.

Author contributions

All authors equally shared in formulating the idea, conception, and data collection statistics, writing and drafting the manuscript.

Acknowledgments

None.

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استخدام الليفوسيمندان في الفترة المحيطة بالجراحة لدى المرضى الذين يعانون من ضعف وظيفة البطين الأيمن والذين يخضعون لجراحة القلب مع المجازة القلبية الرئوية

دراسة عشوائية محكومة

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الخلفية: الغرض من هذه الدراسة هو دراسة تأثير الليفوسيمندان على وظيفة البطين الأيمن لدى المرضى الذين يعانون من انخفاض الوظيفة بعد جراحة القلب المفتوح مع المجازة القلبية الرئوية.

الطرق: شملت الدراسة 120 مريضاً بالغاً خضعوا لجراحة مجازة الشريان التاجي مع أو بدون جراحة الصمام أو جراحة الصمام التاجي المعزولة. وكان جميع المرضى يعانون من ضعف وظيفة البطين الأيمن. في مجموعة الليفوسيمندان (العدد = 60)، تم إدخال المرضى إلى وحدة العناية المركزة قبل الجراحة وبدأ ضخ الليفوسيمندان بعد إدخال خط شرياني قبل 12 ساعة من الجراحة واستمر في غرفة العمليات ثم في وحدة العناية المركزة (إجمالي وقت التسريب 24 ساعة). في مجموعة العلاج القياسية، تمت إدارة المرضى (ن = 60) بالرعاية القياسية وفقًا لبروتوكولنا المؤسسي.

النتائج: تبين أن المرضى في مجموعة الليفوسيمندان لديهم درجة أقل بكثير من التقلص العضلي الوعائي عند 12 و24 و48 ساعة مقارنة بمجموعات المراقبة. علاوة على ذلك، شهدت مجموعة ليفوسيميندان معدلًا أقل بكثير من الرجفان الأذيني السريع، ومدة تنفس صناعي أقصر، و وبقاء في وحدة العناية المركزة والإقامة في المستشفى أقصر.

الخلاصة: الاستخدام الوقائي لليفوسيميندان يحسن وظيفة البطين الأيسر والنتائج الإجمالية لدى المرضى الذين يخضعون لجراحة القلب المفتوح.