Journal of Medicinal and Chemical Sciences 6 (2023) 1433-1443

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Levosimendan versus Dobutamine in Children with Acute Heart Failure

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ARTICLE INFO

Article history

Receive: 2022-09-13
Received in revised: 2022-10-03
Accepted: 2022-11-04
Manuscript ID: JMCS-2210-1824
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Yogesh Tripathi

DOI:10.26655/JMCHEMSCI.2023.6.23

KEYWORDS

Congenital heart disease
Echocardiography
Heart failure
Inotropic drugs

ABSTRACT

Heart failure in children causes substantial morbidity and mortality, so we need an inotropic agent like levosimendan that improves the hemodynamics and relief of symptoms without adverse effects on survival. The aim of this study is to assess the effect of levosimendan vs. dobutamine in children with heart failure. Fifty patients with heart failure caused on by dilated cardiomyopathy, severe critical aortic stenosis, or coarctation of aorta (COA), as well as those who experienced heart failure after cardiac surgery were considered for this study. Patients received either levosimendan or dobutamine infusion for 4-5 days, after they were split into two equal groups. After three months of treatment, the effectiveness of the treatment is evaluated based on changes in the patients' left ventricular (LV) function, heart rate, blood pressure, pulmonary artery (PA) pressure, degree of mitral valve regurgitation, and need for re-hospitalization. The ejection fraction, heart rate, and systolic blood pressure improved in the patients who received the levosimendan and more in those with congenital heart disease of those post-cardiac surgery heart failure. The pulmonary artery pressure and degree of mitral valve regurgitation decreased significantly when levosimendan was used (from 50.92 to 30.38 mmHg and from 80% to 24%, respectively). The period of follow-up for patients of both treatments extended for three months, 15 patients needed another admission in patients on dobutamine infusion, and only 2 patients using levosimendan infusion had needed another admission, no patients developed arrhythmia from those on levosimendan but 6 patients developed arrhythmia in dobutamine group. It was concluded that Levosimendan is an effective drug in improving the survival of children with heart failure, delaying need of extracorporeal membrane oxygenation (ECMO), cardiac transplantation, and decreasing the hospitalization.

GRAPHICAL ABSTRACT

Levosimendan versus Dobutamine in children with acute heart failure


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Introduction

More than 15,000,000 people on the continent of Europe and 5,800,000 people in the USA were projected to have heart failure in 2021 [1-3]. Heart failure is undoubtedly a serious problem with a hospital death rate of about 12% [4-6]. The Inotropic drug had been used for a long period in the treatment of heart failure although these agents have produced a favorable hemodynamic effect, none of these inotropic drugs lead to improvement in symptoms or exercise tolerance and have shortened survival [7].

Inotropes are most frequently utilized in hospitalized patients with the acute decompensated heart failure, reduced left ventricular (LV) ejection fraction, and signs of end-organ dysfunction in the context of a low cardiac output [8–10]. Patients with severe systolic heart failure who are waiting for a heart transplant can utilize inotropes to keep their hemodynamics stable or as a stopgap measure [11].

A common drug in severe heart failure is dobutamine, which not only increases cardiac output, but also myocardial oxygen consumption, increasing the risk of myocardial ischemia and ventricular dysfunction. A recent systematic review suggests that dobutamine may increase mortality [12].

For the treatment of decompensated heart failure (DHF), levosimendan is a calcium sensitizer and vasodilator. As opposed to the other inotropic agents, levosimendan enhances myocardial contractility without increasing myocardial oxygen consumption [13-15] and a recent meta-analysis indicated that levosimendan is effective in reducing mortality in critically ill patients [16-18].

The purpose of this study is to evaluate the effectiveness of levosimendan compared with dobutamine in treating heart failure in children.

Materials and Methods

This study which compared the use of Levosimendan and dobutamine over a period of three years was the first of its kind in Iraq (February 2017-January 2020). All children with acute severe newly diagnosed dilated cardiomyopathy (DCM) or neonates with severe ventricular contractility impairment secondary to critical aortic stenosis or critical coarctation of the aorta (COA) were included, as well as any children in the post-operative state for complex congenital heart disease who developed ventricular dysfunction as a complication for cardiac surgery. These children ranged in age from 1 day to 18 years old. The patients were admitted to pediatric intensive care units (PICU) in Babylon Pediatrics Hospital or CCU in Babylon Cardiac Center. Two pediatric cardiologists performed the echocardiographic studies for all of the patients using vivid E9 (GE Healthcare, Little Chalfont, UK), although none of them were aware of the patients' medication infusion regimens. The echocardiographic examination performed prior to drug delivery, often after 24, 48, 72 hours, 4 and 5 days, and again at 2 weeks, 6 weeks, and 3 months following drug use in conjunction with other conventional heart failure therapy as (diuretic, ACE, Spironolactone). The LV function was determined by M-mode in a parasternal long-axis view, the degree of mitral valve regurgitation assessed by vena-contracta and level of mitral regurgitation (MR) jet extension in left atrium (LA), while the degree of pulmonary hypertension (PHT) was assessed from the degree of tricuspid regurgitation by continuous-wave in four chambers view and added to it the right atrial pressure. The clinical parameter of patients as blood pressure checked twice a day in addition to the continuous ECG monitoring for assessing the changes in the heart and any possible arrhythmia that may be developed, we obtained an informed consent form from parents before the infusion of Levosimendan. To reduce the possibility of bias in the results, we separated the patient into two numerically equal groups. Levosimendan was given to the patient at a dose of 0.1 mcg/kg/min for one day before being increased to 0.2 mcg/kg/min without a loading dose and continued for an additional 4-5 days. The dosage of dobutamine was started at 5 mcg/kg/min and could be increased to 7 mcg/kg/min and continued for the same duration of 3 to 5 days.

We monitored the patient during hospitalization and continued monitoring for three months after discharge.

The statistical analysis was performed using SPSS version 25. Frequencies and percentages were presented for categorical variables. In this study, continuous variables were presented as mean ± standard deviation (SD). Two groups were compared using independent samples t-tests. To compare the means between two paired readings, a paired t-test was used. Categorical variables were analyzed using the Pearson chi-square test and Fisher's Exact test. A p-value ≤ 0.05 was considered as significant.

Results and Discussion

The research continues for three years. Fifty patients were admitted to CCU and PICU with acute severe heart failure of different causes the age of patients ranged from one day to 18 years old and the majority was male as in Table 1.

Congenital heart disease includes critical aortic stenosis, COA, post pulmonary artery (PA) banding in d-transposition of the great arteries (DTGA) with or without ventricular septal defect (VSD), single ventricle surgery (Glenn with PA banding and post- Fontan surgery) in addition to those patients with severe acute dilated cardiomyopathy, patients were divided randomly into two groups with an equal number. The patients receive either levosimendan or dobutamine infusion (Table 2).

The ejection fraction, heart rate, and blood pressure checked frequently before and after treatments in both groups and assess the improvement or deterioration that may be developed, the hemodynamics were improved more with levosimendan than dobutamine and is more with patients with congenital heart disease than the dilated cardiomyopathy regarding the ejection fraction and blood pressure (Tables 3 and 4).

Table 1: Distribution of patients according to study variables (N=50)

Study variables	No.	%
Age (years old)		
< 1 month	11	22.0%
1 month-1 year old	11	22.0%
(1-5) years old	7	14.0%
(5-10) years old	8	16.0%
≥ 10 years old	13	26.0%
Total	50	100.0%
Gender		
Male	29	58.0%
Female	21	42.0%
Total	50	100.0%

Table 2: Distribution of patients according to type of diagnosis in each group

Diagnosis	Types of treatment		Total
	Levosimendan	Dobutamine	
Congenital			
Critical aortic stenosis	2 (18.2)	4 (44.4)	6 (30.0)
Critical Coarctation of aorta	4 (36.3)	3 (33.3)	7 (35.0)
Post Fontan surgery	2 (18.2)	0 (0.0)	2 (10.0)
Glenn+ PA banding	1 (9.1)	0 (0.0)	1(5.0)
DTGA+ PA banding	2 (18.2)	1 (11.1)	3 (15.0)
DTGA+ Large VSD+PA banding	0 (0.0)	1 (11.1)	1(5.0)
Total	11 (100.0)	9 (100.0)	20 (100.0)
Acquired			
Dilated cardiomyopathy	14 (100.0)	16 (100.0)	30 (100.0)
Total	14 (100.0)	16 (100.0)	30 (100.0)

Table 3: The mean differences of study variables according to the type of treatment

Study variables	Study group	N	Mean	SD	T-test	P-value
Ejection fraction (%)	Levosimendan	25	37.48	11.18	2.671	0.01*
	Dobutamine	25	30.48	6.82		
Heart rate (per minute)	Levosimendan	25	109.68	22.79	-5.171	<0.001*
	Dobutamine	25	149.20	30.67		
Systolic blood pressure (mmHg)	Levosimendan	25	82.24	21.42	2.358	0.023*
	Dobutamine	25	69.68	15.82		
Diastolic blood pressure (mmHg)	Levosimendan	25	49.92	14.37	1.665	0.102
	Dobutamine	25	43.96	10.65		

Table 4: The mean differences of study variables according to diagnose in patients receiving levosimendan and dobutamine infusion

Study variables	Study group	N	Mean	SD	T-test	P-value
Levosimendan						
Ejection fraction (%)	Congenital	11	43.72	13.48	2.571	0.024*
	Acquired	14	32.57	5.68		
Heart rate (per minute)	Congenital	11	116.27	27.02	1.300	0.206
	Acquired	14	104.50	18.20		
Systolic blood pressure (mmHg)	Congenital	11	69.72	17.15	-2.985	0.007*
	Acquired	14	92.07	19.60		
Diastolic blood pressure (mmHg)	Congenital	11	41.09	10.73	-3.204	0.004*
	Acquired	14	56.85	13.23		
Dobutamine infusion						
Ejection fraction (%)	Congenital	9	30.77	8.87	0.160	0.874
	Acquired	16	30.31	5.70		
Heart rate (per minute)	Congenital	9	148.33	27.97	-0.104	0.918
	Acquired	16	149.68	32.97		
Systolic blood pressure (mmHg)	Congenital	9	61.00	10.29	-2.524	0.019*
	Acquired	16	74.56	16.54		
Diastolic blood pressure (mmHg)	Congenital	9	38.44	7.09	-2.070	0.05*
	Acquired	16	47.06	11.23		

**P-value ≤ 0.05 is significant*

Compared with dobutamine infusion, levosimendan significantly lowers pulmonary artery pressure (see Figure 1 and Table 5).

No patient of those using levosimendan infusion develop any abnormal rhythm but 6 of patients with dobutamine infusions develop different types of arrhythmias as in Table 6.

Regurgitation of the mitral valve is one of the side effects of heart failure. Before and after both medication infusions, we evaluated whether the regurgitation degree had decreased. The regurgitation degree changed significantly following levosimendan infusion, going from severe to mild to moderate, as seen in Figures 2 and 3. Figure 4 illustrates how many cases of severe regurgitation persist when dobutamine is used.

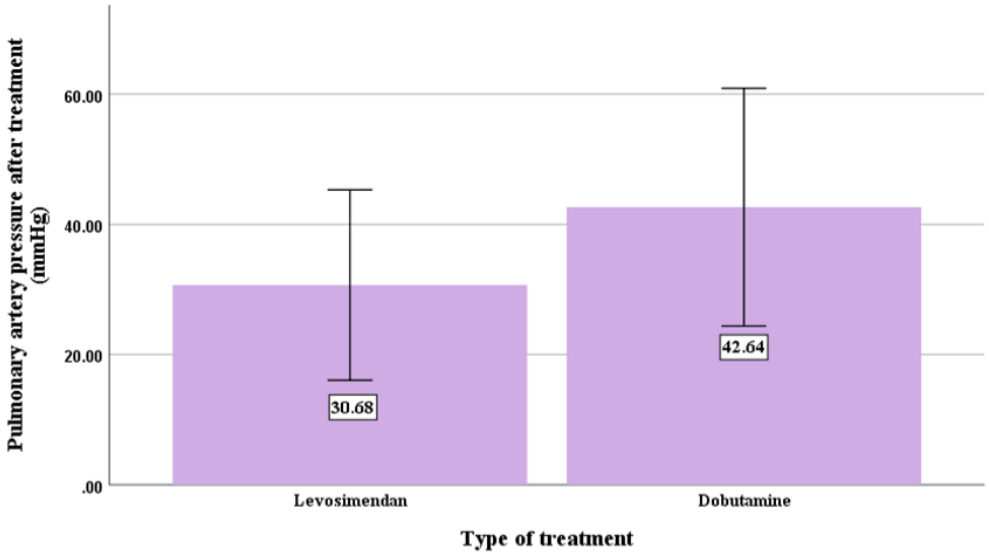

Figure 1: The mean differences of pulmonary artery pressure after use of treatment according to type of treatment

Table 5: The mean differences of pulmonary artery pressure before and after use of Levosimendan treatment

Study variables	Study group	N	Mean	SD	Paired t-test	P-value
Levosimendan						
Pulmonary artery pressure (mmHg)	Before treatment	25	50.92	11.70	10.812	<0.001*
	After treatment	25	30.68	7.30		
Dobutamine infusion						
Pulmonary artery pressure (mmHg)	Before treatment	25	46.96	9.28	3.724	0.001*
	After treatment	25	42.64	9.12		

*P-value ≤ 0.05 was significant

Table 6: Association between study variables and type of treatment

Study variables	Types of treatment		Total	P-value
	Levosimendan	Dobutamine infusion		
Arrhythmia at time of treatment				
Yes	0 (0.0)	6 (24.0)	6 (12.0)	0.022*
No	25 (100.0)	19 (76.0)	44 (88.0)	
Total	25 (100.0)	25 (100.0)	50 (100.0)	
Hospital period /3 months				
1	2 (8.0)	6 (24.0)	8 (16.0)	<0.001*
2	0 (0.0)	6 (24.0)	6 (12.0)	
3	0 (0.0)	3 (12.0)	3 (6.0)	
No	23 (92.0)	10 (40.0)	33 (66.0)	
Total	25 (100.0)	25 (100.0)	50 (100.0)	

**P-value ≤ 0.05 was significant. Fisher's Exact Test.*

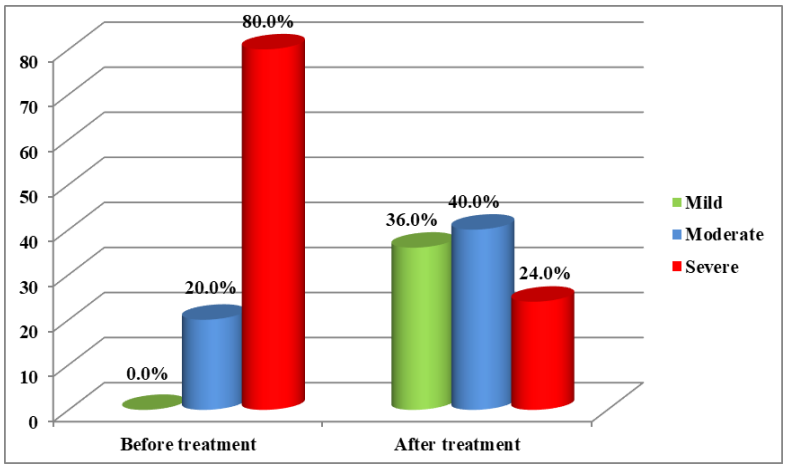

Figure 2: The degree of mitral regurgitation before and after use of levosimendan (N=25)

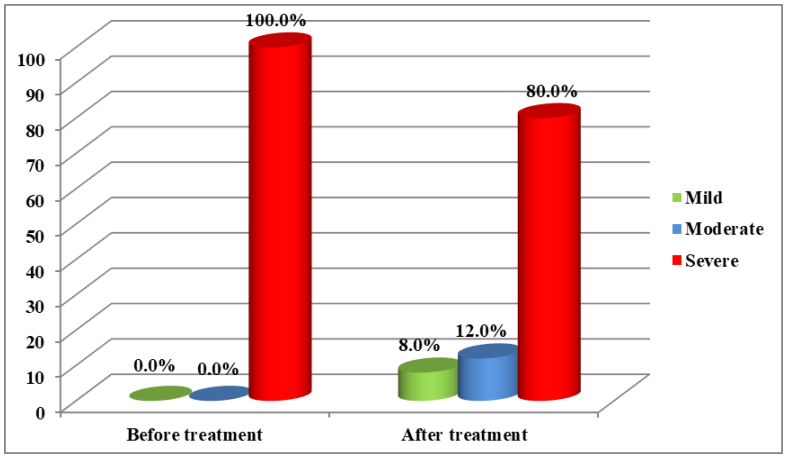

Figure 3: The degree of mitral regurgitation before and after use of Dobutamine infusion (N=25)

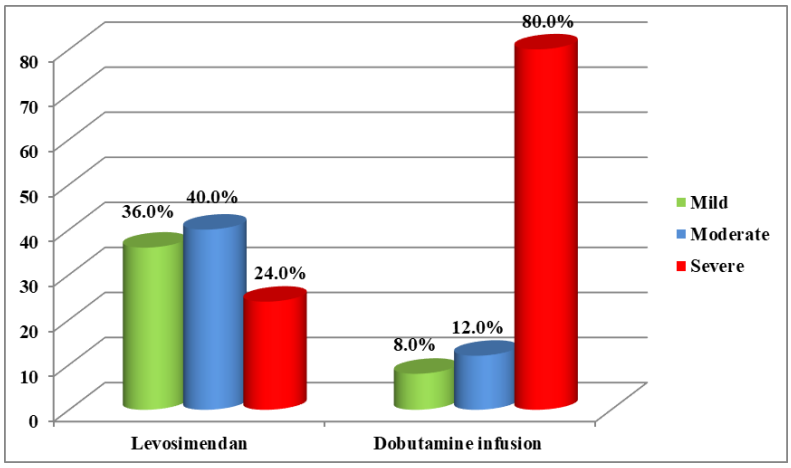

Figure 4: The association between degree of mitral regurgitation after treatment and type of treatment (N=50)

Dobutamine, dopamine, milrinone, and norepinephrine are the oldest drugs that world widely used in acute and chronic severe state heart failure, herein, we compared levosimendan and dobutamine effecting a certain variable in children with severe heart failure these variables either clinical or echocardiographic variables.

We collected the data from children with ages ranged from one day to 18 years old. To prepare the patients for emergency cardiac catheterization or heart failure as a complication

of cardiac surgery, we divided the patients into two groups: those with acquired heart failure and those with congenital heart disease. Boegli *et al.* [17] described using levosimendan as a last resort for cardiac surgery following a failed cardiac catheterization in a neonate with severe critical COA and impaired LV function. We were unable to locate any studies on congenital heart disease patients with LV dysfunction who were undergoing cardiac catheterization to improve their cardiac function, which would have improved the procedure's outcome and reduced their risk of dying, or on post-cardiac surgery patients who developed heart failure weeks or even months after their procedure.

To reduce the possibility of bias, we made the two groups equally composed of patients who, to the greatest extent possible, had the same type of coronary heart disease (CHD). One of these groups received levosimendan, while the other received a dobutamine infusion; this may be the first study of its kind in the pediatric age group. Mebazaa *et al.* [16] did a comparative study, but in the adult age group with acute decompensated heart failure (HF) only.

In this research, we studied clinical variables including the systolic and diastolic blood pressure, heart rate as which improved in patients who received levosimendan infusion. If there is low blood pressure we omitted the loading dose and used only maintenance dose with decrease the dose of diuretics (frusemide) to 0.5 mg/kg /dose and avoid the use of ACE drugs according to the recommendation from Salmenperä and Eriksson [19] in adult literature when the bolus dose was omitted in some unstable hypotensive patients. Levosimendan was used by Nieminen *et al.* [20] in hypovolemic patients. The dose was either temporarily reduced or added vasopressor in place of noradrenalin, and because Levosimendan has a diuretic effect, diuretics were either reduced or stopped a day prior to treatment to prevent unexpected drops in blood pressure. The heart rate was improved which occur as a result of improvement in LV function that will occur after levosimendan infusion especially in those with CHD. Namachivayam *et al.* [21] found there is no change in heart rate, blood pressure, and central venous pressure before and after Levosimendan infusions, but Singh *et al.* [22] evaluated the electrophysiological effect of intravenous levosimendan in healthy volunteers and patient with HF. Levosimendan had no significant effects on heart rate when data were collected from 24 hr. ECG of the patient receiving different doses of drug the heart rate increased at a higher dose. In an adult study by Lilleberg *et al.* [23] assessed the role of levosimendan to produce arrhythmia by studying the ECG recording for one day from 366 patients receiving levosimendan infusion and 142 during placebo found no difference appeared between the two groups in the development of arrhythmia. In our study, no patients receiving levosimendan had any arrhythmia, but six patients receiving dobutamine had ventricular ectopic or sinus tachycardia and supraventricular tachycardia. This can be explained by [20] in treatment of patient of reduced ejection fraction but with recommended dosage (6-24 μg/kg/min rarely produce positive chronotropic exceeding more than 10% from baseline and less markedly in patients with severe heart failure. Therefore, there is a neutral or insignificant effect on heart rate in patients with severe heart failure. With levosimendan as total intracellular calcium level is not raised but sensitizes myofilaments to calcium, which decreases the potential for arrhythmia compared with the other inotropes as catecholamine and phosphodiesterase-3 inhibitor. De Luca *et al.* [24] research reach an agreement that levosimendan less frequently induces arrhythmia compared with Dobutamine.

The other factor that is examined by echocardiographic changes is the ejection fraction, level of mitral valve regurgitation, and pulmonary hypertension. When LV function declines, the LV dilation is the result, and annular dilation of the mitral valve with the development of a different level of mitral valve regurgitation and an increase in LA pressure, pulmonary venous congestion, and ultimately an increase in pulmonary artery pressure. Séguéla *et al.* [25] with children in end-stage heart failure found there is no improvement in Left ventricular ejection fraction (LVEF) after Levosimendan

infusion. The patients chosen were in end-stage heart failure waiting for transplantation. The patient in our study had either acute DCM, acute heart failure following cardiac surgery, or critical CHD. Namachivayam *et al.* [21] used Levosimendan in children with ventricular dysfunction and found there is improvement in LVEF as all from 29.8% to 40.5% which is in line with our study. When compared to dobutamine, patients with CHD who are either pre-catheterization candidates or those who have undergone cardiac surgery are more likely to experience improvement after receiving Levosimendan infusion. The Levosimendan has anti-stunning and anti-ischemic action which is beneficial in those with critical pressure overload on LV and as its action is calcium sensitizer so is the ideal drug in immature myocardium which highly calcium-dependent contractility myocardium and if increase of LVEF to near the normal level lead to decrease the symptom and death during cardiac catheterization and development of arrhythmia. Boegli *et al.* [17] reported using of Levosimendan in a neonate with critical COA with severe LV dysfunction and he noticed an improvement of LV function after these drug infusion. The mitral valve regurgitation depends on the LV function and the pulmonary artery pressure is further depended on the degree of mitral valve regurgitation when the LV size and contractility improve as annular dilation will be improve, the degree of mitral valve regurgitation and pulmonary artery (PA) pressure will decrease and in our study the LV function more correct with those either CHD pre-catheterization preparation or post-cardiac surgery and some patients with dilated cardiomyopathy. Therefore, the degree of mitral valve regurgitation and PA pressure improve more with levosimendan in those groups of patients no study look for the effect of levosimendan on mitral valve function in heart failure. The pulmonary hypertension in acute heart failure secondary to increase of PCWP or secondary to the association of right-sided heart failure with LV failure as Lechner *et al.* [26] post-operative neonate with DTGA who underwent arterial switch operation and suffered from severe ventricular dysfunction and PHT that unresponsive to the other conventional inotropic drug but with good improvement in LV function and decrease in the degree of PHT and LA pressure after Levosimendan infusion. Kleber *et al.* [27], the Levosimendan infusion in 28 adults with PHT most of them secondary to left-sided heart failure found significantly reduced PA pressure and PCWP. The randomized double-blinded study by Ebade *et al.* [28] demonstrated that levosimendan is more effective than the dobutamine in improving cardiac index and lowering the mean pulmonary artery pressure in children younger than 4 years old in our study found a significant lowering of PA pressure after levosimendan infusion as same with other studies. The patient use levosimendan has no more admission to hospital during follow up for three months in regards to those who receive dobutamine infusion who had multiple admission, the explanation that is the levosimendan is led to more improvement in failed heart index that gives the chance for the other conventional cardiac medicine used in heart failure to take its action in maintaining the improvement and decreasing the relapse, this action of levosimendan over the dobutamine because the active metabolite OR,1896, of levosimendan, has long elimination half-life which makes the levosimendan remain active for few days may reaches from 7-9 days The other explanation for decrease the recurrent relapse is the patient with heart failure either with CHD or posts-surgery that improve its function and the effect of cardiac catheterization or surgery in maintenance the stabilization. De Luca *et al.* [24] found that giving intermittent infusion in adults with heart failure after dobutamine infusion every two weeks was associated with improvement of 45 days patient's survival. Lechner *et al.* [26] found that levosimendan cause more improvement in hemodynamics and was associated with a lower risk of death at 31 and 180 days. Compared with the other heart failure medications, levosimendan has a number of benefits for patients with the condition. Levosimendan in adults has been the subject of much research, and it is well understood how the

body uses the medication (pharmacokinetics) and reacts to it (pharmacodynamics) [29-32]. Despite the fact that Levosimendan is increasingly being used in children of all ages, there is a lack of research on its use in children.

Conclusion

Levosimendan is a new promising drug to be used in children with acute or chronic heart failure and to the preparation of patients with critical CHD to cardiac catheterization or cardiac surgery and even in critically ill postoperative cardiac surgery children in PICU or to prepare children for cardiac transplantation to maintain the patient away from extracorporeal membrane oxygenation (ECMO) and mechanical assistance device.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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HOW TO CITE THIS ARTICLE

Mohanad K. Shukur Al-Ghanimi, Khalid A. Khalid. Levosimendan versus Dobutamine in Children with Acute Heart Failure. *J. Med. Chem. Sci.*, 2023, 6(6) 1433-1443

https://doi.org/10.26655/JMCHEMSCI.2023.6.23

URL: http://www.jmchemsci.com/article_160819.html