

Role of inhaled levosimendan in peripartum cardiomyopathy

ABSTRACT

Levosimendan is an inodilator agent, which was initially widely used in low contractility states. However, its use has been restricted because of the invariable need to use a vasoconstrictor like norepinephrine, since it causes a marked fall in systemic vascular resistance (SVR). Hence its beneficial effects on the heart are compromised by the excessive fall in SVR. The inhalational route provides a better opportunity to exploit the positive cardiac effects, with a minimal effect on SVR. In this case report, we present a postpartum patient presenting with heart failure, in which inhalational levosimendan improved the hemodynamics and cardiac function, which was associated with relief of symptoms, with no need for other inotropes. As per our knowledge and extensive literature search, this is the first documented use of inhaled levosimendan in peripartum cardiomyopathy.


Key words: Inhalational route, inodilator, levosimendan, systemic vascular resistance

Background

Levosimendan is a calcium sensitizer, which was widely used as an inodilator agent in low contractility states. However, its use has been restricted because of the invariable need to use a vasoconstrictor like norepinephrine, since it causes a marked fall in systemic vascular resistance (SVR). This is because levosimendan is a non-selective vasodilator. It has the beneficial effect of decreasing pulmonary vascular resistance (PVR), but at the same time has the disadvantage of markedly reducing the SVR. The inhalational route provides a better opportunity to exploit the positive cardiac effects, with a minimal effect on SVR. Here we present a postpartum patient presenting with heart failure, in which inhalational levosimendan improved the hemodynamics and cardiac function, which was associated with relief of symptoms, with no need for other inotropes.

Case Report

A 30-year-old female G₄P₂L₂, term delivery via lower segment cesarean section (LSCS), presented to the Intensive Care Unit (ICU) 24 hours postpartum with respiratory distress. There was no significant past medical history. There were no known peripartum complications like pre-eclampsia. The patient underwent an elective cesarean section under spinal-epidural anesthesia, with the indication being previous LSCS. After delivery of the baby, the patient was given oxytocin in 500 ml normal saline by the Obstetrician. There was no major blood loss in the surgery. The surgery was uneventful. Her intake/output during the surgery was 1500 ml/700 ml. Her fluid balance over 24 hours was +1200 ml. Post-operative electrolytes were also normal.

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PARMINDER KAUR, TANVEER S. KUNDRA¹

Department of Critical Care, Max Hospital Mohali, Punjab, ¹Department of Anesthesiology, Government Medical College Patiala, Punjab, India

Address for correspondence: Dr. Tanveer S. Kundra, Kothi No. 184, Phase 4, Mohali, Punjab - 160 055, India.
E-mail: tvskundra@yahoo.co.in

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On examination, bilaterally decreased air entry and crepitations could be heard on chest auscultation. No murmur was audible on cardiac auscultation. She was having tachycardia with a heart rate of 145 beats/min and was not maintaining saturation on simple oxygen mask with SpO₂ 85% on 10 liters of oxygen. Her blood pressure (BP) was borderline normal (106/60 mm Hg). Electrocardiogram (ECG) did not show any signs of myocardial ischemia. There was no history of any prior cardiac or pulmonary disease. Written informed consent was obtained and the patient was intubated and mechanically ventilated in view of her not maintaining saturation and respiratory distress. Alongside, the patient was given an Inj Frusemide 20 mg intravenously and a 2-D screening echocardiogram was done at the bedside. The patient had very low contractility and severe impairment of LV systolic function (LVEF ~ 25%), suggesting heart failure and fluid overload. A differential diagnosis of postpartum cardiomyopathy, Takotsubo cardiomyopathy, pulmonary embolism, and amniotic fluid embolism was made. Since the BP was borderline, the patient was not put on an intravenous (i.v.) inodilator. Inhaled levosimendan was administered at the dose of 24 mcg/kg via a nebulizer in the inspiratory limb. After some time there was diuresis and the effect of inhaled levosimendan and the patient's clinical condition showed symptomatic improvement. SpO₂ increased to 95%, BP = 124/76 mmHg, PR = 120 beats/min. At no point in time, there was a fall in BP requiring vasopressors, which are to be invariably used along with i.v. levosimendan.

Later on, investigation results were normal except for rise in serum glutamic-oxaloacetic transaminase and serum glutamic pyruvic transaminase levels. Chest X-Ray (CXR) was suggestive of fluid overload. There was mild cardiomegaly on CXR.

A pulmonary artery catheter was inserted from the right internal jugular vein and it revealed an elevated pulmonary capillary wedge pressure (PCWP) = 19 mmHg. The patient was put on intravenous diuretics. Low-molecular-weight heparin was also administered to the patient considering the high risk for thrombo-embolism.

Levosimendan inhalation was repeated 4th hourly for 24 hours and screening 2-D echocardiography was repeated after 24 hours. There was some improvement in cardiac contractility and LV systolic function (EF ~ 30-35%). The patient's hemodynamics improved with a heart rate of 120 beats/min and a BP of 110/70 mmHg. The PCWP and BP measurements pre and post inhalation of levosimendan are shown in [Table 1].

The patient's oxygen requirement decreased and we were able to bring down the FiO₂ to 0.4 by the same night. The

patient was extubated the next day. Post-extubation patient was put on medications which included an angiotensin-converting enzyme (ACE) inhibitor, digoxin, and diuretics. The patient was sent to the ward after 4 days.

Discussion

Heart failure in the peripartum period was first described in 1849. The current diagnostic criteria for peripartum cardiomyopathy (PPCM) include:

1. Cardiac failure in a previously healthy woman in the last month of pregnancy or within 5 months of delivery.
2. Absence of a determinable etiology for cardiac failure.
3. Absence of demonstrable cardiac disease prior to last month of pregnancy.
4. Echocardiographic evidence of diminished left ventricular systolic function.^[1]

Its incidence and prevalence are highly variable depending on the race and geographic regions.^[2]

On investigations, B-type natriuretic peptide and N-terminal proBNP are usually elevated in PPCM, unlike in normal pregnancy.^[1] ECG may show non-specific changes like sinus tachycardia, interventricular delay, and sometimes, left bundle branch block (LBBB) pattern. Chest radiography typically shows pulmonary edema and may show enlarged cardiac silhouette or pleural effusions (or both). Echocardiography suffices to differentiate it from other causes and usually shows left ventricle dilatation of variable degrees, left ventricle systolic dysfunction, right ventricular and bi-atrial enlargement, mitral and tricuspid regurgitation, pulmonary hypertension, and intracardiac thrombus.^[3]

In the present case, the patient fulfilled all the criteria for a diagnosis of peripartum cardiomyopathy. PPCM though rare, has a poor prognosis. It is largely a diagnosis of exclusion. In the present case, the patient presented with an absence of a determinable etiology for cardiac failure.

Table 1: PCWP and BP measurements pre and post inhalation of levosimendan

	PCWP pre inhalation	BP pre inhalation	PCWP post inhalation	BP post inhalation
Dose 1	-	106/60 mmHg	-	100/56 mmHg
Dose 2	19 mmHg	116/74 mmHg	13 mmHg	110/66 mmHg
Dose 3	18 mmHg	124/70 mmHg	13 mmHg	110/74 mmHg
Dose 4	19 mmHg	120/72 mmHg	14 mmHg	110/66 mmHg
Dose 5	18 mmHg	116/66 mmHg	13 mmHg	106/50 mmHg
Dose 6	18 mmHg	128/72 mmHg	13 mmHg	116/74 mmHg
Dose 7	16 mmHg	110/70 mmHg	12 mmHg	102/60 mmHg

The differential diagnosis in the present case includes more commonly seen conditions in the peripartum period such as Takotsubo cardiomyopathy, pulmonary embolism (PE), and amniotic fluid embolism. Takotsubo cardiomyopathy presents as acute heart failure, much the same way as peripartum cardiomyopathy, with management being on the same lines. The difference is that Takotsubo cardiomyopathy will show marked improvement in the 1-month follow-up echocardiography, unlike peripartum cardiomyopathy in which recovery is very slow and incomplete. In PE and amniotic fluid embolism, the saturation usually does not improve even after the application of oxygen.

The sudden decompensation in respiratory status appeared to be the primary issue on presentation. The patient was intubated and mechanically ventilated. Echocardiography revealed the underlying cardiac cause of respiratory decompensation, due to which inotrope was necessary. Other respiratory issues such as bronchospasm and status asthmaticus were ruled out by clinical auscultation and previous history. Amniotic fluid embolus and thrombotic pulmonary embolus were ruled out as saturation increased after intubation and mechanical ventilation.

Treatment of PPCM is usually supportive and directed toward the management of heart failure symptoms.^[4]

In the present case, other inotropic agents could not be used. Dopamine was not preferred due to its arrhythmogenic potential. Dobutamine could not be used due to borderline blood pressure. Epinephrine was not used due to its potential to cause marked tachycardia. Norepinephrine was not preferred as we did not want vasoconstriction in the presence of very low cardiac output.

Inhaled nitric oxide could have been an option, but it requires special equipment for use. Inhaled epoprostenol and inhaled milrinone could have been used but were not preferred due to their short duration of action.

Published data have shown potential advantages of levosimendan in the management of acute decompensated heart failure and advanced heart failure when standard medical therapies threaten hemodynamics and organ perfusion are unable to alleviate clinical symptoms. Levosimendan distinguishes itself from other catecholaminergic inotropes by its three mechanisms of action: positive inotropy, vasodilation, and cardioprotection. In addition, its pharmacokinetics allows for a longer duration of action from the metabolite OR1896 allowing for further cardiovascular therapeutic effects for several days, even after discontinuation of the parent drug.^[5]

Levosimendan, once considered a wonder drug, has fallen in disrepute over the years because of the systemic side effects of intravenous levosimendan, which include a decrease in SVR and systemic hypotension with the invariable need to concurrently use a vasoconstrictor like norepinephrine.

With administration through the inhalational route, levosimendan acts as a selective pulmonary vasodilator and there is minimal effect on SVR, but with the same beneficial effect on pulmonary artery pressure (PAP).^[6] Hence, there is minimal fall in systemic blood pressure. This is a classical example where a drug is not used due to its potential side effects, but a change in the route of administration has provided us with an opportunity to exploit its beneficial effects, bypassing its side effects.

The use of levosimendan via inhalational route is a relatively novel technique and not much literature is available on the same. While SVR was significantly decreased with intravenous levosimendan, there was no significant change in SVR with the use of inhalational levosimendan.^[6]

In another writeup Elhassan *et al.*^[7] (2019) have supported inhaled levosimendan as a novel application to avoid systemic hypotension.

The use of intravenous levosimendan in patients with peripartum cardiomyopathy has had varying outcomes in different studies. Biteker *et al.*^[8] were of the view that the addition of levosimendan to conventional therapy did not improve outcomes in peripartum cardiomyopathy. With the intravenous route there is a marked fall in SVR and it becomes almost impossible to use this drug alone in a patient who is already in cardiogenic shock.

Benlolo *et al.*,^[9] on the other hand, successfully used levosimendan in a patient with peripartum cardiomyopathy. The advantage of levosimendan over other inotropes (eg dobutamine) is that it does not cause an increase in myocardial oxygen consumption.^[10] It does not cause tachyphylaxis. It sensitizes the myocardium to calcium, without actually increasing the calcium influx. Thus it is a very useful drug in cardiomyopathy if its side-effect of excessive peripheral vasodilation can be avoided.

In the present case, we used inhalational levosimendan in a patient with peripartum cardiomyopathy. The drug helped to improve the cardiopulmonary hemodynamics, but an RCT would be needed to evaluate for a mortality benefit.

Conclusion

Inhaled levosimendan is a novel mode of administration of an old drug. This case report suggests a benefit of using inhaled levosimendan and further studies including RCT need to be performed to determine any clinical effect.

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Conflicts of interest

There are no conflicts of interest.

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