

Levosimendan For Post-Partum Cardiomyopathy

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ABSTRACT

Objective: *To describe the use of levosimendan, a novel inotropic agent, for the treatment of post-partum cardiomyopathy (PPCMO).*

Methods: *The authors present the second recorded use of levosimendan for a woman with PPCMO.*

Results: *Levosimendan improved cardiac performance which was associated with symptomatic relief and echocardiographic improvement in ventricular function. The patient recovered from this episode of acute cardiac failure and continues to show steady improvement in cardiac function.*

Conclusions: *Levosimendan proved a useful agent when used as initial therapy in this case of PPCMO. (Critical Care and Resuscitation 2005; 7: 107-110)*

Key words: Levosimendan, post-partum cardiomyopathy

Peripartum cardiomyopathy (PPCMO) is a rare form of congestive cardiac failure of unknown aetiology. Cardiac failure in the peripartum period was first described in 1849,¹ and has been considered a distinct entity since the 1930s.² Current diagnostic criteria for PPCMO include:

1. development of cardiac failure in a previously healthy woman in the last month of pregnancy or within 5 months of delivery,
2. absence of a determinable aetiology for the cardiac failure,
3. absence of demonstrable cardiac disease prior to the last month of pregnancy, and
4. echocardiographic evidence of diminished left ventricular systolic function.^{3,4}

We report a case of a young woman presenting with cardiac failure following delivery of healthy twins. She was treated successfully with levosimendan (Orion Corporation, Espoo, Finland), a new calcium sensitising agent with inotropic and vasodilator properties.⁵

CASE REPORT

A 30 year-old Caucasian woman (para 1, gravida 3) at 36 weeks of gestation with monochorionic, diamniotic twins was admitted to hospital for induction of labour for discordant growth of twin pregnancy. On admission, the maternal heart rate was 70 beats per

minute (bpm) and regular, blood pressure (BP) was 118/60 mmHg. Foetal heart rates were 140 bpm and 135 bpm. After artificial rupture of membranes and 3 hours of stimulation of labour with an oxytocin infusion, twin I weighing 2680 g was born by vaginal delivery. The second twin, weighing 1805 g, was born 10 minutes later by breech extraction. Following completion of the third stage of labour, Syntocinon (Oxytocin, Novartis Pharmaceuticals Australia, North Ryde, Australia) 10 IU was given by intramuscular injection.

Thirty minutes after delivery of the second twin the patient complained of escalating chest tightness and palpitations, associated with dyspnoea, light-headedness, nausea and vomiting. She was reviewed by her obstetrician, who requested her immediate transfer to the Intensive Care Unit (ICU). The differential diagnosis at this time included undiagnosed cardiac disease (ischaemic or valvular), pulmonary oedema (fluid overload), amniotic fluid embolus or drug reaction.

On arrival in the ICU, the patient had a thready and irregular pulse (60 bpm), an elevated blood pressure (170/90 mmHg), dyspnoea (30 shallow breaths/min) and was hypoxaemic (difficulty maintaining oxygen saturation above 88 percent, despite the administration of oxygen at 10 L/min via face mask). The patient was cyanosed and had mild peripheral oedema. Auscultation

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of her chest revealed dual heart sounds with no murmurs. There was decreased air entry at both lung bases, with inspiratory crackles throughout. The abdomen was soft and non-tender with a firm and contracted uterus. An electrocardiogram (ECG) showed sinus arrhythmia, but no evidence of myocardial ischaemia. Systematic questioning revealed no previous history of cardiac or pulmonary disease. Laboratory investigations showed a haemoglobin level of 139 g/L with normal leukocyte and thrombocyte counts. Serum electrolytes, renal function and thyroid function were all normal. Lactate dehydrogenase was raised at 556 U/L. There were no foetal squames in the maternal circulation. Chest radiograph (CXR) showed bilateral interstitial infiltrates with a left pleural effusion of moderate size. The heart size was normal.

Central venous and arterial catheters were placed. Transthoracic echocardiography revealed severe impairment of left ventricular systolic function. There was a global decrease in contractility with left ventricular fractional shortening of 15% and moderate mitral and tricuspid regurgitation. A diagnosis of PPCMO was made.

Central venous pressure and mean arterial blood pressure read 12 and 130 mmHg respectively. Intravenous frusemide (40 mg, Hoechst Marion Roussel Australia, Lane Cove, Australia) was administered without clinical improvement. A continuous levosimendan infusion was then initiated at 0.1 µg/kg/min, without a preceding loading dose. This was continued for 24 hours. After 6 hours the patient's symptoms had largely resolved. The pulse was again regular (70 bpm), blood pressure stable (110/60 mmHg) and she was maintaining an oxygen saturation of 96% on 3 L/min supplemental oxygen via nasal prongs. Serum cardiac enzyme levels 4 hours post admission to the ICU were normal (troponin T <0.01 µg/l and CK <195 U/L).

Angiotensin-converting enzyme inhibitor (ACEI) (ramipril 2.5mg oral daily, Hoechst Marion Roussel Australia, Lane Cove, Australia) and diuretic (frusemide 40 mg oral daily) therapy were commenced on the second day and the patient continued to improve. Laboratory investigations 12 hours after arrival in the ICU showed a raised serum troponin T level of 0.44 µg/L. Carvedilol (3.125 mg oral daily, Roche Products, Dee Why, Australia), spironolactone (25 mg oral daily, Pharmacia Corporation, Chicago, U.S.A.) and digoxin (125 µg oral daily, GlaxoSmithKline, Research Triangle Park, USA) were initiated and titrated with careful attention to blood pressure. Given the risk of thromboembolism the patient was anticoagulated initially with intravenous unfractionated heparin, then warfarin. The patient continued to improve, while laboratory and radiographic investigations normalized over the ensuing

days. She was discharged from the ICU after 5 days and then home 9 days later. Echocardiography performed 5 days after ICU admission showed much-improved left ventricular function (graded as "moderate impairment"), with only trivial mitral, tricuspid and aortic valve regurgitation. The ECG was normal. Future pregnancies were discouraged and risks discussed with our patient.

DISCUSSION

PPCMO occurs in 1:2400 to 1:15 000 pregnancies. It remains one of the leading causes of maternal morbidity and mortality in developed countries. Fifty percent of patients have resolution of cardiomegaly and congestive cardiac failure within 6 months. The remaining 50 percent experience persistent cardiac dysfunction, with 85 percent mortality over an average 4.7 years.^{4,6} The aetiology of PPCMO remains unknown, however risk factors include:⁷

- age over 30 years,
- multiparity,
- black race,
- multiple gestation,
- obesity,
- pre-eclampsia and
- chronic hypertension.

Whether PPCMO represents a distinct clinical entity or the unmasking of subclinical or compensated heart disease remains unclear.⁴ The normal cardiovascular changes of pregnancy, which include an increase in cardiac output by 30-50% during pregnancy with a further 10-40% during labour, may contribute to peripartum cardiac failure in predisposed patients.^{8,9} Important complications of PPCMO are systemic and pulmonary embolism from mural thrombus and cardiac arrhythmias.

The clinical presentation of PPCMO is similar to that of other forms of left ventricular systolic dysfunction. Patients often present with chest pain, dyspnoea, fatigue, and palpitations, as in our patient. Other symptoms can include orthopnoea, paroxysmal nocturnal dyspnoea, cough, peripheral oedema, and haemoptysis. Physical examination can be significant for signs of right and left cardiac failure. Most patients present in New York Heart Association (NYHA) Class III or IV cardiac failure.¹⁰ Routine investigations should include ECG, CXR, and echocardiography.^{11,12} The ECG may show normal sinus rhythm or sinus tachycardia, but may also show non-specific changes including ventricular hypertrophy and sinus arrhythmia, as was the case in our patient. CXR often exhibits cardiomegaly with left ventricular enlargement, pulmonary oedema, and bilateral pleural effusions. Echocardiography is essential, not only to assist in diagnosis, but also to exclude other causes of cardiac

failure, such as valvular heart disease.

Our patient fulfilled the criteria for PPCMO, including acute onset cardiac failure shortly after delivery, absence of pre-existing heart disease or cause for sudden deterioration, and echocardiographic evidence of dilated left ventricular failure (fractional shortening 15 percent with left atrial size 4.3 cm). To make the diagnosis of PPCMO, all other causes of left ventricular dysfunction must be excluded; such as myocardial infarction, sepsis, severe pre-eclampsia, pulmonary embolism (thrombus or amniotic fluid), idiopathic dilated cardiomyopathy, and valvular heart disease (mitral or aortic stenosis). Myocardial infarction is a possible additional diagnosis in our patient given the raised cardiac enzyme levels. However, in the absence of any known risk factors for ischemic heart disease this was less likely. Amniotic pulmonary embolism was unlikely in our patient given the absence of foetal squames in the maternal circulation.

Traditional therapy for PPCMO is similar to that of other forms of congestive cardiac failure in pregnancy. This includes mainly symptom control, aiming at reduction in after-load and pre-load and augmentation of myocardial contractility. After-load reduction can be achieved with ACEI, which is generally reserved for the post-partum period due to its unwanted effects on the foetus. Diuretics, considered safe in pregnancy, are used for pre-load reduction and symptom relief. Digoxin is also safe in pregnancy and is used for enhancing contractility and rate control. Thrombo-prophylaxis with heparin, as was provided to our patient, should be considered on a case-by-case basis.

As conventional acute treatment for cardiac failure did not yield early clinical improvement in our patient, we opted for levosimendan, a member of a new class of agents called calcium channel sensitizers, instead of resorting to dobutamine or adrenaline. Levosimendan improves myocardial performance by directly acting on contractile proteins, without increasing intracellular calcium and its effects. Increased intracellular calcium is an unavoidable side effect of traditional inotropes (catecholamines or phosphodiesterase inhibitors) that increases myocardial oxygen demand and the risk of arrhythmia. Levosimendan also leads to vasodilatation through the opening of ATP-sensitive potassium channels in vascular smooth muscle. Improved contractile performance and vasodilatation leads to a reduction in both pre-load and after-load. An additional advantage is that the drug and its metabolites have a prolonged duration of action, even after discontinuing the infusion.

Although relatively new, two studies have shown haemodynamic and symptom improvement as well as benefits in morbidity and mortality with the use of levosimendan in acute cardiac failure. The RUSLAN

study,¹³ showed patients receiving levosimendan experienced lower risk of death and worsening cardiac failure compared with those receiving placebo. This was maintained at 14 days and at 180 days. The LIDO study,¹⁴ compared levosimendan infusion with dobutamine in patients with low output cardiac failure. Greater haemodynamic improvement at 24 hours and lower mortality at 180 days was observed in patients receiving levosimendan. However, there is limited experience with the use of levosimendan in PPCMO as this is only the second reported use of the agent in this situation.¹⁵

In the patient with PPCMO, failure of the heart to return to its normal size within 6 months is a poor prognostic indicator. Currently there is no consensus regarding recommendations for future pregnancy after PPCMO.¹⁶ However, most authors agree that subsequent pregnancies should be discouraged or avoided, especially when the left ventricular function has not returned to normal.¹⁷

CONCLUSIONS

PPCMO is an uncommon, but life-threatening, condition that strikes in the prime of a young woman's life. Data about PPCMO is very limited owing to the great variability in the natural course of the disease. While traditional therapies for acute cardiac failure continue to be employed, levosimendan is a promising new agent that may prove a useful addition to the treatment of PPCMO. When treated with levosimendan shortly after giving birth to her twin daughters, our patient showed steady clinical and echocardiographic improvement. She ultimately recovered from this acute cardiac failure and continues to show improvement towards normal cardiac function.

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