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Brief Report

Continuous inhaled iloprost in a neonate with D-transposition of the great arteries and severe pulmonary arterial hypertension

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Abstract This report describes the case of a neonate with D-transposition of the great arteries and severe pulmonary arterial hypertension stabilised in the post-operative period with continuous iloprost nebulisation. To our knowledge, this is the first documented method of treating post-operative severe pulmonary arterial hypertension with continuous inhaled iloprost in a patient with complex CHD. We found this method of delivering the drug very effective in stabilising haemodynamic swings in the setting of severe pulmonary arterial hypertension.

Keywords: Inhaled iloprost; pulmonary arterial hypertension; transposition of the great arteries; CHD

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D-TRANSPOSITION OF THE GREAT ARTERIES WITH pulmonary arterial hypertension is a well-described entity with significant morbidity and mortality. Attempts have been made to aggressively treat these patients both medically and surgically in the neonatal period with varying degrees of success.[1] After oxygen and inhaled nitric oxide, three main therapies for pulmonary arterial hypertension include phosphodiesterase inhibitors, endothelin receptor antagonists, and prostacyclins.[2,3] Each of these therapies carries significant risks, drug interactions, and costs. Prostacyclin therapy can be very effective in treating pulmonary arterial hypertension, but in the past could only be administered intravenously.[4] Inhaled iloprost, a prostacyclin analogue, now exists with a few case studies documenting its potential role in intubated neonatal patients with pulmonary arterial hypertension;[5] however, its short half-life of <30 minutes necessitates frequent administrations, as often as every 1–3 hours, adding substantially to drug costs and logistical issues related to frequent dosing.[5,6]

Case report

We present the case of a female neonate born at 38 weeks of gestation via caesarean section to a 21-year-old woman with no prenatal diagnosis of CHD. Shortly after birth, the baby was intubated for hypoxia and was started on prostaglandin therapy. An echocardiogram was performed and revealed the following anatomy {S,D,D} transposition of the great arteries with intact ventricular septum, a patent ductus arteriosus with bidirectional shunting, a floppy moderately stretched patent foramen ovale with bidirectional shunting, and good biventricular function. A balloon atrial septostomy was performed immediately after birth due to hypoxia. The baby was subsequently sedated, paralysed, and started on inhaled nitric oxide at a dose of 40 parts per million. Despite this maximal medical therapy, the patient continued to clinically deteriorate with worsening arterial saturations. The decision was made to correct her anatomy in an effort to more effectively treat her pulmonary arterial hypertension in the post-operative period. The patient was urgently taken for an arterial switch operation on day of life 3 with a patent foramen ovale left as a pop-off in the setting of pulmonary arterial hypertension. She returned to the CICU on inhaled nitric oxide, milrinone, sedation, and neuromuscular blockade agents. Her post-operative echocardiogram showed systemic right ventricular pressures with fair biventricular systolic function. The patient soon developed evidence of intermittent pulmonary arterial hypertension spells with simultaneous drops in systemic oxygen saturations

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and systemic blood pressure. To support our haemodynamic assessment, we utilised the Equanox Cerebral Oximetry System (Nonin Medical Inc., Plymouth, Minnesota, United States of America). Using this technology, it was our consistent observation that with each pulmonary arterial hypertension event there was a sudden drop in cerebral near-infrared spectroscopy values with a less dramatic decrease in systemic oxygen saturation (rSO_2). This suggested an increased arteriovenous oxygen difference, indicating an acute decrease in cardiac output. Along with 100% FiO_2, inhaled nitric oxide at 40 parts per million, and initiation of intravenous vasopressin for systemic hypotension, the patient was placed on intravenous sildenafil and epoprostenol; however, sildenafil and epoprostenol had to be discontinued due to systemic hypotension and worsening ventilation–perfusion mismatch, respectively. On post-operative day 3, the patient was started on inhaled iloprost at 5 mcg per dose with dramatic clinical improvement as evidenced by higher systemic oxygen saturations, higher cerebral near-infrared spectroscopy values, and improved blood pressure stability. This was confirmed by serial echocardiographic assessments of right ventricular pressure surrounding iloprost administration. At baseline, the child had a right ventricular pressure of 75% systemic, which fell to 35% at 5 minutes post treatment. Nevertheless, these benefits were transient with right ventricular pressures of 46% systemic at 30 minutes and 82% at 1 hour post treatment. In an effort to help avoid these severe and frequent life-threatening haemodynamic swings, continuous inhaled iloprost was initiated. To accomplish this, 30 mcg of iloprost was diluted in 30 ml of normal saline to create a 1 mcg/ml solution, which was infused via an inline jet nebuliser at a rate equivalent to 5 mcg/hour. After initiation, there was a clear stabilisation of systemic blood pressure, a sustained improvement in systemic arterial saturations, and near-infrared spectroscopy values (Fig 1). Before continuous inhaled iloprost therapy (time 00:00 on Fig 1), the child was receiving 10 mcg/hour (iloprost 5 mcg every 30 minutes) with frequent swings in haemodynamics. After transitioning to continuous inhaled iloprost therapy with half the hourly dose (5 mcg/hour), we observed higher average near-infrared spectroscopy values with no significant life-threatening swings in haemodynamics. Furthermore, the lowest near-infrared spectroscopy value only minutes after transitioning to continuous iloprost was 69 versus 45 with intermittent dosing. After several days of continuous inhaled iloprost therapy, her right ventricular pressures dropped to less than half systemic as determined by echocardiography. The patient was weaned off continuous iloprost 18 days later followed gradually by all the other pulmonary arterial hypertension therapies. Despite the prolonged high doses of iloprost, our patient did not show any of the common known side-effects such as systemic hypotension or bronchospasm. Unfortunately, despite the resolution of her severe pulmonary arterial hypertension, the patient remained in the hospital for a prolonged period due to idiopathic recurrent chylothorax. After several failed medical and surgical attempts to treat the chylothoracies, the child passed away due to overwhelming infection and respiratory failure.

Discussion

In a single recent series, transposition of the great arteries with intact ventricular septum had a much higher incidence of pulmonary arterial hypertension

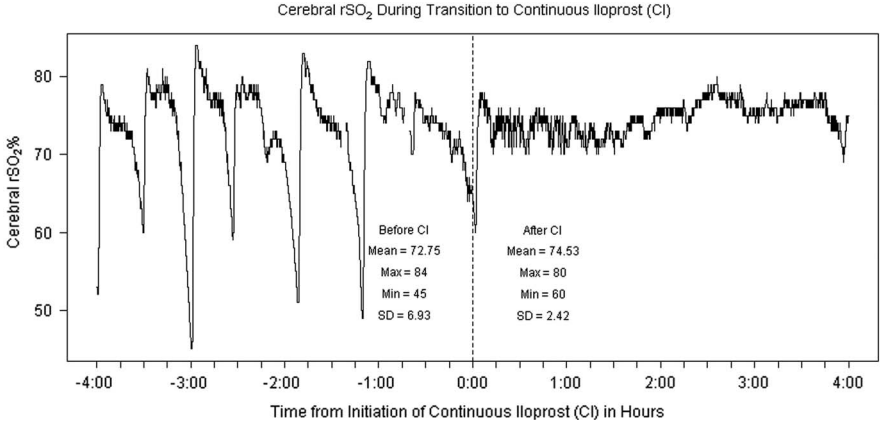

Figure 1.
Cerebral rSO_2 values collected from Equanox Cerebral Oximetry System (Nonin Medical Inc., Plymouth, Minnesota, United States of America) during the transition from intermittent inhaled iloprost to continuous inhaled iloprost (time 0:00). To the left of time 0:00, the baby was receiving intermittent inhaled iloprost 5 mcg every 30 minutes. To the right of time 0:00, the baby was placed on CI infused via an inline jet nebuliser at a rate of 5 mcg/hour.

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(15.6%) compared with transposition of great arteries with a ventricular septal defect (3.4%). The overall mortality of patients with transposition of the great arteries and pulmonary arterial hypertension was 28.6%, despite optimal conventional therapy including inhaled nitric oxide and adequate balloon atrial septostomy.[1] Mainstays of treatment for neonates with pulmonary arterial hypertension consist of sedation, optimised ventilation, oxygen, and inhaled nitric oxide. Recently, endothelin receptor antagonists such as bosentan and ambrisentan, phosphodiesterase inhibitors such as sildenafil and tadalafil, and prostanoids such as epoprostenol, treprostinil, and iloprost have demonstrated some promise in a few paediatric studies.[2] Each therapy has unique side-effects and drug interactions that must be considered. Inhaled therapies offer the benefit of minimising ventilation–perfusion mismatch by exerting favourable effects on those parts of the lung that are ventilated.[7] Oxygen, inhaled nitric oxide, and the prostacyclin analogue iloprost are three inhaled therapies available at present in the United States to treat pulmonary arterial hypertension.[2,3,5] Prostacyclin was described more than 20 years ago to be a potent platelet inhibitor and vasodilator agent. The half-life of prostacyclin is ~20–30 minutes, and the recommended dose per day is between six and nine treatments of 5 mcg per dose (45 mcg per day).[3,6] The benefits or safety issues of increased doses remain uncertain.[5]

To our knowledge, this is the first published case of an infant with complex CHD and severe pulmonary arterial hypertension stabilised with continuous inhaled iloprost. In this patient's case, the drug was proven to be very effective, but only when high doses were administered in a continuous inhaled infusion.[5,6] Although our patient did not show any side-effects of the increased dose, further studies are needed to evaluate the safety profile of this method of delivery in children with CHD and severe pulmonary arterial hypertension.

In summary, this neonate with D-transposition of the great arteries and severe pulmonary hypertension refractory to all traditional first-, second-, and third-line therapies did not demonstrate significant clinical improvement until continuous inhaled iloprost was included to standard pulmonary arterial hypertension therapies. With half the daily dose delivered in a continuous manner, we were able to achieve a more stable haemodynamic profile, decrease the charged medication cost by 50%, and ultimately wean off the medication with significantly decreased pulmonary artery pressures by echocardiography and cardiac catheterisation. We believe that this single case report demonstrates that continuous inhaled iloprost therapy might have a role in the acute treatment of some neonates with complex CHD and severe pulmonary arterial hypertension refractory to more traditional therapies.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all the procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by Nicklaus Children's Hospital Designated Reviewers.

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