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CASE REPORT

Inhaled Iloprost as a Rescue Therapy for Transposition of the Great Arteries With Persistent Pulmonary Hypertension of the Newborn

Alejandro Avila-Alvarez · Maria Carmen Bravo-Laguna · Lucía Deiros Bronte · Maria Jesus Del Cerro

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Abstract Transposition of the great arteries (TGA) in the newborn combined with persistent pulmonary hypertension was reported previously to occur in 3–12 % of full-term neonates with TGA. Right-to-left shunting at the ductal level causes severe hypoxemia despite prostaglandin infusion and balloon atrial septostomy. Although the introduction of inhaled nitric oxide (iNO) has improved the prognosis, this condition still is associated with high preoperative mortality. This report describes the case of a newborn with TGA and persistent pulmonary hypertension, which was managed successfully with oral sildenafil, iNO, and inhaled iloprost during life-threatening acute pulmonary hypertension, thus preventing the use of extracorporeal membrane oxygenation.

Keywords Iloprost · Persistent pulmonary hypertension of the newborn · Prostacycline · Transposition of great vessels

Introduction

Transposition of the great arteries (TGA) is the most common cyanotic congenital heart defect encountered in neonates. The standard approach in the neonatal period includes prostaglandin (PGE1) administration, a balloon atrial septostomy (BAS) if adequate mixing is not present at the atrial level, and an arterial switch operation within the first weeks of life. Although this approach has improved the survival of the affected neonates, up to 4 % die before surgery [11].

Persistent pulmonary hypertension of the newborn (PPHN), resulting from the failure of the vascular bed to decrease its resistance after birth, affects 0.2 % of term infants [3]. Although PPHN has been described as an idiopathic entity, it also has been associated with sepsis, meconium aspiration, congenital diaphragmatic hernia, and congenital heart diseases.

The combination of TGA and PPHN (TGA-PPHN) leads to profound hypoxemia, even in the presence of a wide ductus arteriosus and a successful BAS. This association was reported previously with an incidence of 3–12 % of patients with TGA [7, 10]. Although the introduction of inhaled nitric oxide (iNO) has dramatically improved the outcome of these patients, TGA-PPHN still is associated with much higher mortality than simple TGA [4, 10].

We report the case of a neonate who presented with TGA-PPHN and was treated successfully with a combination of pulmonary vasodilator agents, including inhaled iloprost, during life-threatening pulmonary hypertensive crises.

Case Report

A full-term infant with a birth weight of 4,170 g was admitted to our unit with a prenatal diagnosis of TGA and a restricted foramen ovale. At the infant's arrival, profound cyanosis was observed, with a preductal oxygen saturation (SpO_2) of 40 % and a postductal SpO_2 of 65 %. An

A. Avila-Alvarez (✉) · M. C. Bravo-Laguna
Neonatal Intensive Care Unit, Department of Neonatology, Hospital Infantil Universitario La Paz, Paseo de la Castellana, 261, 28046 Madrid, Spain
e-mail: alexavila81@hotmail.com

L. D. Bronte · M. J. D. Cerro
Department of Pediatric Cardiology, Hospital Infantil Universitario La Paz, Madrid, Spain

intravenous infusion of PGE1 was started to maintain ductal patency.

The postnatal echocardiographic findings were concordant with the prenatal diagnosis (D-TGA with an intact ventricular septum). A restricted foramen ovale and a continuous shunt from the pulmonary artery to the aorta at the ductal level were observed, suggesting elevated pulmonary vascular resistance.

An emergency BAS was performed in the first hour of life, obtaining a nonrestrictive 6-mm interatrial communication, and a transient improvement in oxygenation was observed. However, in the hours immediately after the BAS, the patient remained severely hypoxemic (with a preductal SpO_2 of <60 % and a postductal SpO_2 of <75 %) despite mechanical ventilation, fentanyl and midazolam sedation, vecuronium neuromuscular blockade, 100 % inspired oxygen, moderate hyperventilation, iNO therapy (20 ppm), inotropic support with dopamine, and volume expansion.

At 10 h of life, the infant's the SpO_2 worsened abruptly, with a preductal SpO_2 as low as 20 %, a postductal SpO_2 as low as 60 %, and systemic hypotension. Echocardiography showed continuous right-to-left shunting across the ductus arteriosus. Given the lack of response to the aforementioned therapies, we administered inhaled iloprost (Ventavis; Bayern Schering Pharma AG, Berlin, Germany) by connecting an ultrasound nebulization chamber to the inspiratory branch of the ventilator circuit (Aeroneb module for Servo-I ventilator; Maquet Critical Care AB, Solna, Sweden), thus preventing disconnection from the respirator. We introduced 10 μg of iloprost into the nebulizer and diluted it in 3 ml of normal saline to obtain a dose of 1.2 μg delivered through the endotracheal tube. Once the iloprost was nebulized, oxygen saturation rose immediately to 85 %, with no pre-postductal gradient and no systemic hypotension.

After the acute episode of pulmonary hypertension was resolved, we administered sildenafil (0.5 mg/kg every 8 h) through the nasogastric tube. In the following hours, iloprost was administered twice in the setting of profound acute hypoxemia with a reversed SpO_2 gradient. A rapid and favorable response was observed in both instances.

Over the subsequent days, the patient remained stable with sildenafil and iNO. No additional pulmonary hypertensive crises were noted. The iNO treatment was decreased gradually and then withdrawn before surgery.

Corrective surgery (arterial switch operation) was performed at 9 days. The postoperative course was uncomplicated. Supplementary oxygen was administered for 3 days, and no other pulmonary vasodilators were required. The infant was discharged from the neonatal intensive care unit (NICU) on postoperative day 7 after a normal neurologic examination.

Discussion

The current standard approach to preoperative TGA with an intact ventricular septum aims to promote adequate mixing of oxygenated and deoxygenated blood. If a restrictive foramen ovale is present, a BAS must be performed. Often, PGE1 infusion is required in the first hours of life to provide an extra amount of pulmonary blood flow, thus promoting left-to-right shunting at the atrial level. Untreated, TGA is a fatal disease that leads to heart failure and death within the first months of life, but with current therapies, TGA patients usually have a good prognosis.

By contrast, mortality increases significantly in the setting of associated PPHN [7, 10]. In this situation, the shunting across the ductus arteriosus is bidirectional or even right to left, with oxygenated blood passing to the lower body and poor interatrial mixing. This starts a "vicious circle," with hypoxemia and acidosis further increasing the pulmonary vascular resistance. Clinically, this condition is detected with reversed differential cyanosis (a higher SpO_2 in the legs than in the upper body).

The incidence of TGA-PPHN is reported to be 3–12 % of all TGA cases [7, 10], which is significantly higher than the incidence of PPHN in otherwise healthy full-term newborns, suggesting that TGA-PPHN is more than the sum of both conditions. Most likely, the influence of a restricted foramen ovale or premature constriction of the ductus arteriosus promotes in utero changes in the pulmonary vascular bed that lead to a failure in normal pulmonary vascular adaptation after birth [8, 10]. In fact, necropsy studies have found severe intimal hyperplasia and medial hypertrophy in the pre-acinar arterioles [7]. It also is well known that hypoxemia and acidosis, which often present with TGA after birth, can cause pulmonary vasoconstriction and thus an increase in pulmonary vascular resistance [4].

The current management of PPHN includes mechanical ventilation, supplementary oxygen, blood pressure optimization, appropriate sedation, and pulmonary vasodilators, mainly iNO. Pulmonary vasodilators are described to be effective in some patients with TGA-PPHN. In fact, the introduction of iNO has yielded encouraging results in this group of patients [4, 10]. Although iNO therapy is considered the first choice in neonates with PPHN, approximately 30 % fail to respond. Interestingly, in the largest series of TGA-PPHN, reported by Roofthooft et al. [10] in 2007, all the patients with severe PPHN who were nonresponders to iNO died in the preoperative period. In this group of severe PPHN patients, the mortality rate was as high as 50 %. The authors concluded that despite the introduction of iNO, TGA-PPHN remains a condition with unacceptably high mortality and that additional therapies therefore need to be investigated.

Other strategies have been reported in the literature. Goissen et al. [5] described successful treatment with bosentan, an oral endothelin-1 receptor antagonist, in two cases of PPHN complicating TGA. The administration of intravenous vasodilators (e.g., tolazoline, epoprostenol) also has been reported for this condition [5, 10], but the systemic effects in neonates, particularly during hypercyanotic crises in which hypotension typically is present, may limit their use. Sildenafil, a type 5 phosphodiesterase inhibitor, has been shown to improve oxygenation in infants with PPHN [12] and can be used as an adjunct therapy to iNO.

Prostacyclin is an important mediator of pulmonary vasodilation and may play an important role during adaptation to extrauterine life. Findings have shown iloprost, a prostacyclin analog, to be effective as a rescue therapy for PPHN [1, 2]. However, as stated in a recent review, clinical data regarding its use in neonates remain scarce, and the optimal dose for neonates and infants has not been established to date [9].

Direct lung administration of iloprost by connecting a nebulization system to the ventilator circuit could avoid or attenuate some systemic adverse effects, particularly hypotension [2]. However, establishing the optimal dose for neonates is difficult because the amount of iloprost that must be introduced into the nebulizer for a given target dose differs depending on the nebulizing system, and these data are not always described in the literature.

Extracorporeal membrane oxygenation (ECMO) has been proposed as a rescue treatment for patients with TGA-PPHN that is unresponsive to conventional therapies. Jaillard et al. [6] reported that preoperative venoarterial ECMO reversed pulmonary hypertension in a full-term neonate with TGA-PPHN, but it is noteworthy that this patient also had severe biventricular dysfunction shown by echocardiography. The morbidity associated with ECMO in the neonatal population, particularly neurologic complications, makes it reasonable to search for therapeutic alternatives before considering extracorporeal support. Some concern also exists about the left ventricle "deconditioning" after preoperative mechanical support in TGA.

In the reported patient, the combination of iNO and oral sildenafil, with iloprost administered during acute pulmonary hypertension episodes, was associated with an improvement in oxygenation, resulting in a good preoperative condition and thereby avoiding the use of ECMO. To our knowledge, this is the first reported case of iloprost used for patients with TGA-PPHN.

In conclusion, iloprost may have a role in the acute management of neonates with TGA-PPHN when the standard therapies have failed. Iloprost, particularly in combination with other pulmonary vasodilator drugs, may be an effective alternative to ECMO during pulmonary hypertensive crises in TGA-PPHN.

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