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Nitric oxide in neonatal transposition of the great arteries

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Abstract

Three newborn infants with transposition of the great arteries (TGA) and intact ventricular septum (IVS) developed postnatal persistent pulmonary hypertension of the newborn (PPHN) and were successfully treated with inhaled nitric oxide (iNO). Intervention with balloon atrial septostomy (BAS) was performed in two of the infants before the iNO treatment, but they continued to be severely hypoxic with metabolic acidosis. However, the iNO immediately improved oxygenation and the clinical condition. The third neonate had a moderately large atrial communication and echocardiographic signs of PPHN. He received iNO before BAS with dramatic clinical improvement, which therefore postponed BAS.

Conclusion: Early diagnosis of PPHN and treatment with iNO may improve final outcome in neonates with TGA and IVS. In the presence of moderately large atrial communication and PPHN, treatment with iNO might be considered before BAS.

Key Words: *Atrial septostomy, intact ventricular septum, nitric oxide, persistent pulmonary hypertension of the newborn, transposition of the great arteries*

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a well-known cause of morbidity and mortality in full-term and near-term infants. Management of this condition has been greatly improved by the use of inhaled nitric oxide (iNO), especially when limited to patients with severe extrapulmonary shunting [1–5]. Transposition of the great arteries (TGA) and intact ventricular septum (IVS) is associated with development of neonatal pulmonary hypertension in 4% of cases [6]. Preoperative mortality in neonates with TGA has been reported to be 4%, and among these, PPHN was a contributing factor in 17% of preoperative deaths [7]. Preoperative management with prostaglandin E_1 (PGE_1) and balloon atrial septostomy (BAS) is not sufficient to improve oxygenation in some infants with TGA and PPHN [6]. Luciani et al. reported a successful management protocol using iNO and extracorporeal membrane oxygenation in two neonates with TGA and PPHN [6].

Previous reports have stressed the risks associated with PPHN in infants with TGA, including high mortality, but fewer reports have discussed possible treatment strategies [7]. To illustrate possible preoperative strategies in infants with TGA, IVS and PPHN, we report three infants who did not respond to BAS and the usual supportive managements. In all three infants, administration of iNO resulted in prompt improvement in oxygenation and clinical condition.

Patients and methods

The Children's Hospital at Lund University Hospital is one of two Swedish referral centres for paediatric cardiac surgery. During an 18-mo period, between January 2001 and June 2002, 22 neonates with TGA were referred for preoperative and surgical management. Thirteen of the 22 infants (59%) had TGA and IVS, and nine (41%) had TGA with ventricular septal defect (VSD). Seven of the 13 infants with TGA and IVS underwent BAS. Three babies (14%) had a complicated course with profound hypoxia and acidosis. They developed pulmonary hypertension early after delivery and were successfully treated with iNO (AGA Medical system).

Case 1

On his first day of life, a full-term male infant, born at 42 wk of gestation, with a birthweight (BW) of 3765 g

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and normal Apgar scores, developed cyanosis with oxygen saturation 60%, arterial pH 7.1 and base excess (BE) −10.4. Cardiac echocardiography demonstrated TGA and IVS and a small patent foramen ovale (PFO). Intravenous infusion with PGE_1 was started (50 ng/kg/min). He was transported without complications to the cardiac centre. On admission, he was clinically stable, with oxygen saturation 70%, and ongoing PGE_1 infusion. There was no cardiac murmur, and neurological status was normal. A repeated echocardiographic examination confirmed the diagnosis TGA and IVS. Soon after arrival, his clinical condition deteriorated with increasing respiratory distress, and mechanical ventilation was started. Despite the ventilatory support, oxygen saturation declined from 70% to 50%. An emergency BAS was done with maximum balloon size 2 ml, but there was no clear improvement in oxygenation, which remained around 60%. After a few hours, oxygen saturation deteriorated to less than 50% and metabolic acidosis developed (BE −8.4). Cardiac echocardiography showed signs of PPHN with shunt flow through the patent ductus arteriosus (PDA) from the pulmonary artery to the descending aorta. In spite of supportive measures, no improvement occurred in oxygen saturation, which remained around 55%, and the infant also developed arterial hypotension. Volume support with transfusions of blood and fresh frozen plasma was given, and dopamine infusion (2–5 μg/kg/min) was started. These changes rendered some improvement in the oxygen saturation (65%). Muscle tone increased but there were no convulsions, amplitude-integrated EEG monitoring (Cerebral Function Monitor, CFM, Lectromed, Letchworth, UK) showed normal electrocortical background activity [8]. Midazolam and morphine infusions were given for sedation.

Several hours later, oxygenation deteriorated again. A new echocardiography of the heart showed signs of continued pulmonary hypertension. Inhaled nitric oxide was started with 20 parts per million (ppm), and oxygen saturation rose immediately and stabilized at 85% within 4 h. A repeated cardiac echocardiography showed that the flow through the PDA was now completely reversed, i.e. from the descending aorta to the pulmonary artery. The iNO treatment could therefore be decreased and was discontinued within 24 h. As no more neurological symptoms were noted, no further neurological investigations were performed, and the midazolam and morphine infusion were discontinued. Corrective surgery was performed at 7 d with an arterial switch operation (ASO). The postoperative course was uncomplicated, and the infant was discharged home on postoperative day 10. He has developed normally on follow-up at 3 y of age, and no cardiac or neurological complications have been reported.

Case 2

Initial clinical examination after birth of a full-term male baby, with BW 3680 g and normal Apgar scores, showed cleft lip, cyanosis, and oxygen saturation of 50% in the arms and 75% in the feet. On cardiac auscultation, there was no murmur. A cardiac malformation was suspected, PGE_1 infusion was started and the baby was transported with ongoing mechanical ventilation to the cardiac centre at 8 h postnatal age. On admission, he was clinically stable with oxygen saturation 60%, pH 7.2 and BE −8. Cardiac echocardiography revealed TGA and IVS, a patent foramen ovale with left-to-right shunting, and a large PDA with bi-directional shunt flow, mainly from the aorta to the pulmonary artery. An emergency BAS, with achievable balloon size 3.5 ml, was performed since oxygen saturation had deteriorated to 45%. Immediately after BAS, oxygen saturation increased to 80% and mean arterial blood pressure rose from 35 mmHg to 54 mmHg. Five hours later, oxygen saturation deteriorated to 45% again. A repeat echocardiography of the heart showed a large atrial septal defect (ASD) with left-to-right shunt, and a large PDA with shunting from the pulmonary artery to the descending aorta, indicating PPHN. Inhaled NO was started with 20 ppm resulting in immediate improvement in oxygen saturation, which increased to 80%. Two hours later, repeat cardiac assessment by echocardiography showed shunt direction through the PDA from the descending aorta to the pulmonary artery. The iNO treatment was gradually decreased and could be withdrawn after 8 h without complication. An ASO was performed at 5 d postnatal age. The infant continued to be stable after surgery, and he was discharged home at 2 wk of age. On follow-up control at 1 y of age, he had developed normally and no cardiac or neurological complications had been reported.

Case 3

In a full-term male infant, with BW 3630 g and normal Apgar scores, cyanosis was evident 15 min after delivery. Oxygen saturation was 80%, pH 7.18 and BE −6. He was admitted to the neonatal unit and received treatment with continuous positive airway pressure (CPAP), FiO_2 50% and sodium bicarbonate buffer. However, there was no improvement in his oxygen saturation, which initially remained at 80%, and 2 h later decreased to 50%. Mechanical ventilation and PGE_1 infusion was started. The initial PGE_1 dose was 50 ng/kg/min, but since this dose did not result in improved oxygenation the dose was increased to 100 ng/kg/min. However, oxygen saturation remained around 65%, and the baby was transported to our cardiac centre by an emergency team.

On admission, his oxygen saturation was 80% with 100% inspired oxygen. Cardiac and pulmonary

auscultation was normal, as were peripheral pulses and a chest X-ray.

The PGE_1 dose was reduced to 50 ng/kg/min. Cardiac echocardiography demonstrated a TGA and IVS and a moderately large atrial communication with diameter 7 mm. During preparation for BAS, at 5 h of age, his condition deteriorated with poor peripheral circulation, hypothermia (body temperature 35°C), and oxygen saturation decreased to 50%. He also developed "reversed differential cyanosis", i.e. a demarcation line on the chest at the level of the nipple, with darker skin colour on the upper part of the body and paler skin colour on the lower part of the body. A new cardiac evaluation by echocardiography revealed signs of PPHN with shunt flow through the PDA from the pulmonary artery to the descending aorta. Inhaled nitric oxide was started with an initial dose of 10 ppm and then increased to 20 ppm. Oxygen saturation rose from 50% to 60% within 20 min, and then gradually increased to 80–85%. The differential cyanosis disappeared gradually, and the baby's general condition stabilized. A repeat echocardiography showed that shunt direction through the PDA was bi-directional with flow dominance from the descending aorta to the pulmonary artery. With this improvement, it was concluded that BAS was not vitally needed since an ASO was planned within a few days. The iNO treatment was gradually withdrawn and discontinued after 12 h. The PGE_1 dose was reduced to 20 ng/kg/min with maintained oxygen saturation around 85–88%. One day later, the baby had increased muscle tone but no signs of clinical convulsion. EEG showed normal background activity with some sharp waves. A CT scan of the brain showed ischaemic changes, indicating focal infarctions in the left hemisphere of the brain. Clinical convulsions occurred and were treated with phenobarbitone and phenytoin. At this stage, a cardiopulmonary bypass operation was concluded to imply too much risk on brain function, and surgery was consequently postponed. Oxygenation and haemodynamic variables stabilized, and the infant was extubated from mechanical ventilation. BAS was performed at 9 d of age. At 18 postnatal days, a new CT scan and brain MRI showed no new cerebral ischaemic lesions, and no progress in those previously described. It was possible to perform ASO at 25 d of age with good result. Postoperatively, the baby continued with phenobarbitone treatment for 3 mo. Both cardiac and neurological status were normal on later follow-up at 3 y of age.

Results

Details of the clinical courses, e.g. oxygen saturation and shunting directions, for the three infants are given in Table I and Figure 1. Arterial blood gases, including methaemoglobin levels, were checked frequently at a few-hour intervals. None of the infants developed methaemoglobinaemia. There were no rebound effects in oxygen saturation after withdrawal of iNO treatment.

Discussion

We have described the positive effects of iNO in three neonates with TGA and IVS who developed PPHN. The addition of iNO to the conventional treatment gave an immediate and striking improvement in oxygenation.

It is well known that the combined effect of acidosis and hypoxaemia may cause intense pulmonary vasoconstriction, raise pulmonary vascular resistance, and in newborns with TGA and IVS this may result in PPHN. Despite early PGE_1 treatment, which keeps

Table I. Clinical and diagnostic details of patients.

No.	Clinical	Echo finding	Before BAS	After BAS	Before iNO	After iNO	Comments
1	Cyanosis, acidosis	TGA & IVS PFO	Sat 50% PaO_2 1.9 BE −3.9 PGE_1, PDA flow PA→DA	Sat 60% PaO_2 2.0 BE −8.4	Sat 50% PaO_2 3.8 BE 1.9 PDA flow DA→PA	Sat 85% PaO_2 4.7 BE 1	Response to iNO <4 h. Operated at 7 d.
2	Cyanosis, acidosis	TGA & IVS PFO	Sat 45% PaO_2 2.9 BE −7.3 PGE_1, PDA flow PA→DA	Sat 80% PaO_2 2.7 BE 1.6	Sat 45% PaO_2 2.7 BE −1.9 PDA flow DA→PA	Sat 85% PaO_2 4.5 BE −0.9	Immediate response to iNO. Operated at 5 d.
3	Cyanosis, acidosis	TGA & IVS PFO/ASD (7 mm)	Not done PGE_1, PDA flow PA→DA		Sat 50% PaO_2 2.8 BE −6.2 PDA flow DA→PA	Sat 85% PaO_2 4.7 BE −1.3	Immediate response to iNO. Operated at 25 d.

BAS: balloon atrial septostomy; iNO: inhaled nitric oxide; TGA: transposition of the great arteries; IVS: intact ventricular septum; PFO: persistent foramen ovale; ASD: atrial septal sefect; Sat: oxygen saturation; PaO_2: partial pressure of oxygen in arterial blood in kPa; BE: base excess; PGE_1: prostaglandin E_1; PDA: patent ductus arteriosus; PA: pulmonary artery; DA: descending aorta.

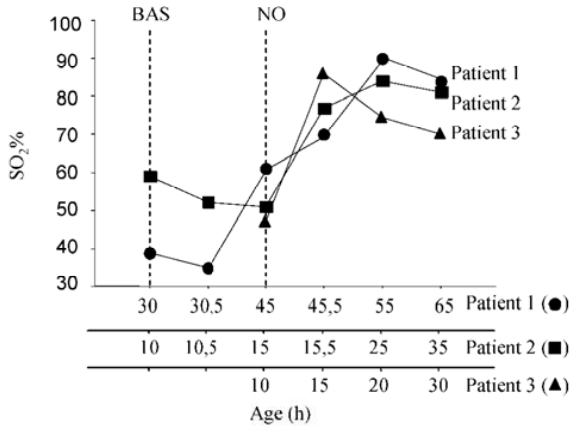

Figure 1. Blood oxygen saturation before and after BAS and iNO. Oxygen saturation was persistently improved only after iNO treatment.

the ductus arteriosus open, and BAS, which may create large interatrial communications, some of the newborn infants with TGA have limited intercirculatory mixing. As iNO creates pulmonary vascular relaxation, more blood reaches the pulmonary capillaries. This changes haemodynamics through facilitated interatrial mixing and thus increases arterial oxygenation. Inhaled nitric oxide does not change cerebral blood flow, or cerebral oxygen consumption [9].

The use of iNO in treatment of PPHN with severe extrapulmonary shunting was reported in two previous studies [4,5]. In newborn infants with PPHN, the clinical response to iNO seems to be most dramatic in patients with the most severe hypoxaemia when initiating the treatment [10].

The three infants in the present report developed cyanosis early after delivery, and further investigations confirmed the diagnosis of TGA and IVS. They were all outborn, and after initial stabilization, including PGE_1, they were transported to our cardiac centre. The clinical condition of newborns with cardiovascular and/or pulmonary disease may deteriorate during long-distance transportation. During a 5-y period, almost 50% of infants with TGA arrived with oxygen saturation less than 65% [11]. To improve outcome from emergency transfers, urgent bedside balloon atrial septostomy in the local neonatal intensive units might be performed by a mobile specialist cardiac team [12]. This management would probably also reduce the risks for development of PPHN in some of the infants, since early BAS is likely to improve oxygenation and thus prevent prolonged acidosis and hypoxaemia.

Reversed differential cyanosis, i.e. a line of demarcation on the chest wall at the nipple level where the cyanosis of the upper body was greater than that of the lower body, was present in one of the infants. In infants with TGA and IVS, the presence of reversed differential cyanosis indicates that the blood flow through the ductus arteriosus is directed from the pulmonary artery to the aorta, and consequently that PPHN may be present. However, reversed differential cyanosis is not specific for PPHN in infants with TGA; it can also be found in more complex cardiac malformations with aortic anomalies [13].

Two of the presented infants developed clinical neurological symptoms. In one infant, there was mild muscle rigidity with spontaneous regress within 4 to 5 h. In the other infant, there was increased muscle rigidity and clinical convulsion; EEG showed increased sharp wave activity but no seizure activity, and CT and MRI showed cerebral infarction. It is likely that the cerebral ischaemic lesions developed during the initial severe hypoxaemia and acidosis, before iNO treatment was started.

After the initial critical course, all three infants were treated surgically with ASO without any perioperative complications. None of the babies developed post-operative pulmonary hypertension, which is a described risk [14]. Furthermore, long-term neurological follow-up was normal in all three children.

In conclusion, the acute management of neonates with TGA and IVS, early diagnosis of PPHN and treatment with iNO may improve outcome in these infants. In the presence of moderately large atrial communication and PPHN, treatment with iNO should be considered before BAS.

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References

[1] Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:818–9.
[2] Milner AD. Nitric oxide. Eur J Pediatr 1994;153 Suppl 2:S7–11.
[3] Roberts JD, Jr, Fineman JR, Morin FC, 3rd, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med 1997;336:605–10.
[4] Kinsella JP, Abman SH. Clinical pathophysiology of persistent pulmonary hypertension of the newborn and the role of inhaled nitric oxide therapy. J Perinatol 1996;16 Suppl:S24–7.
[5] Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev 2001(4):CD000399.
[6] Luciani GB, Chang AC, Starnes VA. Surgical repair of transposition of the great arteries in neonates with persistent pulmonary hypertension. Ann Thorac Surg 1996;61:800–5.
[7] Soongswang J, Adatia I, Newman C, Smallhorn JF, Williams WG, Freedom RM. Mortality in potential arterial switch candidates with transposition of the great arteries. J Am Coll Cardiol 1998;32:753–7.
[8] Thornberg E, Thiringer K. Normal pattern of the cerebral function monitor trace in term and preterm neonates. Acta Paediatr Scand 1990;79:20–5.

[9] Rosenberg AA, Kinsella JP, Abman SH. Cerebral hemodynamics and distribution of left ventricular output during inhalation of nitric oxide. Crit Care Med 1995;23:1391–7.

[10] Parker TA, Kinsella JP, Abman SH. Response to inhaled nitric oxide in persistent pulmonary hypertension of the newborn: relationship to baseline oxygenation. J Perinatol 1998; 18:221–5.

[11] Hellstrom-Westas L, Hanseus K, Jogi P, Lundstrom NR, Svenningsen N. Long-distance transports of newborn infants with congenital heart disease. Pediatr Cardiol 2001;22:380–4.

[12] Martin AC, Rigby ML, Penny DJ, Redington AN. Bedside balloon atrial septostomy on neonatal units. Arch Dis Child Fetal Neonatal Ed 2003;88:F339–40.

[13] Ochikubo CG, Waffarn F, Turbow R, Kanakriyeh M. Echocardiographic evidence of improved hemodynamics during inhaled nitric oxide therapy for persistent pulmonary hypertension of the newborn. Pediatr Cardiol 1997;18:282–7.

[14] Richter JA, Barankay A. Pulmonary hypertension and right ventricular dysfunction after operations for congenital heart disease. Acta Anaesthesiol Scand Suppl 1997;111:31–3.