Original Article Indian J Pediatr 1999; 66 : 357-361

Role of Inhaled Nitric Oxide as a Selective Pulmonary Vasodilator in Pediatric Cardiac Surgical Practice

K.S. Murthy, Suresh G. Rao, K. Shiva Prakash, C. Robert, S. Dhinakar and K.M. Cherian

Institute of Cardio Vascular Diseases, Madras Medical Mission, Mogappair, Chennai

Abstract : Our aim was to assess the role of inhaled nitric oxide (NO) therapy in post operative cases of congenital heart defects who developed pulmonary arterial hypertensive (PAH) crisis and had no response with conventional management. From February '95 to January '97, inhaled NO therapy was used in 21 children. Age ranged from 2 months to 9 years (mean 5.6 years) and duration of therapy ranged from 1 to 13 days. Of 21 patients, 17 responded well with 5-20 ppm while 4 did not. The preoperative mean pulmonary systolic pressure was 88 mm Hg against mean systemic pressure of 96 mm Hg. Post operatively, their PA pressure reduced to 62 mm Hg, with systemic pressure of 98 mm Hg. After using inhaled NO, PA pressure dropped to 24 mm Hg (mean systolic) ($p < 0.007$), after excluding the non responders. Of 4 non responders, two died due to irreversible pulmonary vascular disease and remaining two died due to residual defects. The study shows that inhaled NO is a selective pulmonary vasodilator, which is useful in postoperative PAH crisis and also reduces the transpulmonary gradient in single ventricle repair cases. It is safe and effective for prolonged use. It is very useful in Indian perspective, when more number of cases with congenital heart defects (CHD) alongwith severe PAH are encountered routinely. **(Indian J Pediatr 1999; 66 : 357-361)**

Key words : *Inhaled nitric oxide; Selective pulmonary vasodilator; Paediatric cardiac surgery; Congenital heart defects; Pulmonary hypertensive crisis.*

Some children after congenital heart repair develop a post operative critical rise of pulmonary pressure which is otherwise called pulmonary arterial hypertensive (PAH) crisis. It is further exacerbated by cardio pulmonary bypass (CPB). PAH crisis complicates the post operative management and increases the morbidity and mortality.

Conventional vasodilators are often non selective for PAH and may produce systemic hypotension and can cause deleterious effects. A specific endothelium derived relaxation factor (EDRF) was isolated by Furchgott in 1980[1] and it was subsequently identified as nitric oxide (NO)[2,3]. Recent reports have suggested that inhaled NO is a selective pulmonary vasodilator in PAH cases both in children and adults. Developing countries like India get more cases of delayed and neglected children with congenital heart disease associated with severe PAH. Our aim was to assess the role of inhaled NO therapy post operatively in children who developed PAH crisis and who showed no response with conventional management.

Reprint requests : K.S. Murthy M.S., M.Ch., Consultant Cardiac Surgeon, Institute of Cardio Vascular Diseases, Madras Medical Mission, 4A J.J. Nagar, Mogappair, Chennai - 600 050

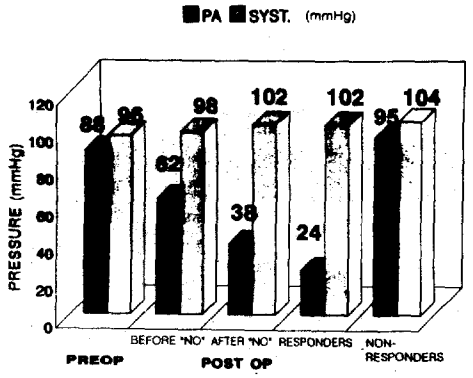

Fig. 1. Pre and post operative haemodynamic data

Table 1. Clinical Spectrum

Total number of cases	=	21
dTGA, VSD	=	5
VSD +/- ASD, PDA	=	5
Complete AV canal defect	=	4
TAPVC	=	3
Redo TAPVC	=	1
Single ventricle repair	=	3

METHODS AND MATERIALS

This study was conducted from February 1995 through January 1997. Inhaled NO therapy was used in 21 cases with age range from 2 months to 9 years (mean = 5.66 years). Clinical spectrum is given in Table 1. Post operatively, heart rate and arterial, pulmonary, left atrial, central venous pressures and arterial blood gases and urine output were monitored.

Inhaled NO therapy was used post operatively in cases of failure of conventional management of PAH crisis and transpulmonary gradient more than 10 mm Hg in single ventricle repair cases. Transpulmonary gradient is the pressure difference between RA and LA and 5-10 mm Hg pressure difference is acceptable. More than 10 mm Hg indicates a high pulmonary vascular resistance). The conventional management of PAH crisis included use of high FiO_2 (> 0.8) maintain PaO_2 > 200 mm Hg and $PaCO_2$ < 30 mm Hg with deep sedation, analgesia and muscle paralysis. Patients were hyperventilated, hourly, with 100% oxygen for 5-10 minutes. Inhaled NO therapy was started with 5 ppm and increased to 20 ppm to get maximum response. It was increased to 120 ppm in two cases.

NO delivery and its toxic end product nitrogen dioxide (NO_2) were monitored continuously with B & W Medimax electrochemical sensors. Methemoglobin levels were monitored every morning and evening. Exhaled limb of the ventilator was connected to a scavenging system, since NO is a toxic gas in high concentrations (> 50,000 ppm). The attending staff were instructed to follow certain precautions such as to protect their skin with gowns and gloves, eyes with glasses while doing endotracheal (ET) suction. They were also advised not to use contact lenses during this procedure. Ventilation was weaned along with reduction of NO concentration, when there was no PAH crisis for 6 hours in the face of ET suction, weaning of sedation and reduction in FiO_2.

NO inhalation was used from 1 to 13 days (mean 3.2).

RESULTS

Seventeen of the twenty one patients responded well to inhaled NO while 4 patients did not. Their preoperative mean PA (systolic) pressure was 88 mmHg against

mean systemic (systolic) pressure of 96 mmHg. Post operatively, their PA pressure dropped to 62 mmHg (mean), before starting NO therapy. After NO inhalation, their overall PA pressure (mean systolic) fell to 38 mmHg with improvement in systemic pressure. After excluding the non responders from responders, the PA pressure came down to 24 mmHg ($P < 0.007$) (Fig. 1). Four patients who did not respond to inhaled NO died postoperatively. First patient had redo surgery for suspected stomal obstruction, for supracardiac total anomalous pulmonary venous connection (TAPVC) repair. Intraoperatively, it was found that there was no stomal obstruction. Second patient was a 3 year old child with complete atrioventricular canal defect with severe PAH. Post operative echo showed no significant AV valve regurgitation and no residual shunt across the patch. In both the patients PA pressure did not reduce even after increasing the NO concentration to 120 ppm and sometimes even went up to suprasystemic pressure which was a paradoxical response. They died post operatively, probably with irreversible pulmonary vascular disease. The third postoperative patient of VSD closure did not respond to inhaled NO therapy. Postoperative echocardiogram showed a significant residual VSD. He succumbed to death before he was taken up for reoperation. The fourth patient had fenestrated total cavopulmonary connection (modified Fonton procedure) for single ventricle and pulmonary stenosis. Post operatively, he developed low cardiac output with increased transpulmonary gradient. He was put on inhaled NO therapy. He did not survive due to significant subaortic stenosis which was detected postoperatively. The toxic end product, NO_2 was monitored continuously and was never more than 2 ppm (> 5 ppm is toxic). Methemoglobin levels were monitored to less than 1 gm%, morning and evening.

DISCUSSION

PAH crisis complicates the post operative management and often increases the morbidity and mortality. Traditional vasodilators are non selective for pulmonary hypertension. Recent reports have suggested that inhaled NO (EDRF) is a selective pulmonary vasodilator. Inhaled NO diffuses directly into smooth muscles of pulmonary vasculature. It directly activates guanylate cyclase which increases intracellular cyclic guanosine 3, 5 monophosphate levels in smooth muscle cells and produces pulmonary vasodilatation[4]. Then it diffuses into pulmonary vascular lumen, where it gets inactivated by reacting with hemoglobin and forms nitrosyl and methemoglobin[5]. This explains the selective action on pulmonary vasculature.

Our study showed that inhaled NO is useful in postoperative cases of PAH crisis and in high transpulmonary gradient patients who fail to respond with conventional management. Seventeen of the twenty one patients who responded with 5-20 ppm of NO therapy survived and did well postoperatively, which was similar to the results reported by Dider Journois[6] and Ronald D. Currian[7]. Wessel et al[8] investigated the effects of acetylcholine (endothelium dependent vasodilator) and inhaled NO (endothelium derived relaxation factor) in pediatric patients with CHD and severe PAH. They demonstrated that the vasodilatory response to an intrapulmonary infusion of acetylcholine was markedly attenuated after CPB. In contrast, inhaled NO, after CPB, lowered pulmonary vascular re-

sistance by 33% and resulted in a 3 fold increase in plasma cyclic guanosine monophosphate levels. These data demonstrate that inhaled NO is an effective pulmonary vasodilator in postoperative cases of CHD. Further, the pathophysiology of postoperative PAH may, in part, be due to CPB induced endothelial dysfunction.

Our experience showed that if there was no response to inhaled NO in lower oncentration (5-20 ppm), there would not be any response with higher doses (120 ppm) as well[9]. Similar findings were reported by Miller[10] and Ronald D. Curran[7]. Two patients, redo TAPVC correction and complete AV canal repair, did not respond with high concentration of inhaled NO. Their postoperative echocardiogram showed good correction. These two patients died probably with irreversible pulmonary vascular disease. The postoperative echocardiogram of the third and fourth patients who did not respond with NO showed residual defects. Before they were taken up for redo correction, they succumbed to death. The end products nitrogen dioxide and methemoglobin never went above the toxic levels even after using NO for 13 days.

Our study demonstrates that inhaled NO is useful as a selective pulmonary vasodilator in postoperative cases of PAH crisis and reduces the transpulmonary gradient in single ventricle repair cases. Additionally it is useful in persistent foetal circulation[11], diaphragmatic hernia[12], respiratory distress syndrome[13]. Even though there are several indications for using inhaled NO, selective use is maintained for postoperative cases of CHD with severe PAH as there are severe constraints in importing the gas. Inhaled NO therapy was introduced in India by the Madras Medical Mission which still remains the only centre using it so far.

Conclusion

Inhaled NO is useful in postoperative cases of PAH crisis, refractory to conventional management and also reduces the transpulmonary gradient in single ventricle repair cases. It is safe and effective for prolonged use. In patients who do not respond with inhaled NO, one should look for correctable residual problems. If they do not have any significant residual cause for high PAH, they may be having irreversible pulmonary vascular disease. It is very useful in Indian perspective where large number of cases of CHD with severe PAH are encountered routinely.

REFERENCES

1. Furchgott RF, Lawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; 288 : 373-376.
2. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biologic activity of endothelium-derived relaxation factor. *Nature* 1987; 373 : 524-526.
3. Ignarro L, Buga G, Woods K, Byrns R, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci* 1987; 84 : 9265-9269.
4. Ignarro L. Biological actions and properties of endothelial derived nitric oxide formed and released from artery and vein. *Cir Res* 1989; 65 : 1-21.
5. Gruetter C, Gruetter G, Lyon J, Ignarro L. Relationship between cyclic guanosine 3, 5-monophosphate formation and relaxation of coronary arterial smooth muscle by glyceryl trinitrate, nitroprusside, nitrite and nitric oxide. *J Pharmacol Exp Ther* 1981; 219 : 181-6.
6. Journois D, Ponard P, Mauriat P, Malahere T, Vouhe P, Safran D. Inhaled nitric oxide as a therapy for pulmonary hypertension

after operations for congenital heart defects. *J Thorac Cardio Vasc Surg* 1994; 107; 1129-1135.

7. Curran RD, Mavroudis C, Becker CL, Sautel M, Lales VR, Wessel DL. Inhaled nitric oxide for children with congenital heart disease and pulmonary hypertension. *Ann Thorac Surg* 1995; 60 : 1765-71.
8. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardio-pulmonary bypass. *Circulation* 1993; 88 : 2128-38.
9. Murthy KS, Suresh Rao, Shivaprakash K *et al.* Inhaled nitric oxide as therapy for pulmonary hypertension in postoperative cases of congenital heart defects. *Indian Heart Journal.* 1996; 48 : 695-698.
10. Miller OI, Cehrmajer DS, Dreanfield JE, Macral DJ. Very low dose inhaled nitric oxide as a selective pulmonary vasodilator after operations for congenital heart disease. *Thorac Cardio Vasc Surg* 1994; 108 : 487-94.
11. Roberts JD, Polaner DM, Lang P, Zapal WM.Inhaled nitric oxide in persistant pulmonary hypertension of the new-born. *Lancet* 1992; 340 : 818-9.
12. Shah N, Jacob T, Exler R, Morrow S, Ford H, Albanese C *et al.* Inhaled nitric oxide in congenital diaphragmatic hernia. *J Pediatr Surg* 1994; 29 : 1010-1005.
13. Rossaint R, Halke KJ, Lopez F, Llama K, Pison U, Zapor WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Eng J Med* 1993; 328 : 399-405.

PERSISTENT COUGH IS OFTEN MISDIAGNOSED AS WHEEZE

A study was conducted in Australia to determine if children in the community with persistent cough can be considered to have asthma. The study included 1245 randomly selected children aged between 6 and 12 years. A validated questionnaire was given to their parents.

Atopy was measured with skin prick tests to eight common allergens (2 house dust mites, grass, 2 species of molds, cats and cockroaches). It was defined as a wheal size of 3 mm or more to any of the allergens. Recent wheeze was defined as the presence of wheeze or exercise wheeze in the previous 12 months.

Persistent cough was defined as the presence of a cough lasting for more than 3 weeks without cold or flu in the previous 12 months. It was found that children with persistent cough had less morbidity and less atopy as compared to those children with wheeze. A no. of children were identified who had been diagnosed as having wheeze and had been given asthma medications including inhaled steroids. At this juncture, the problem related to cough variant asthma has been discussed, and it is suggested that this is a misnomer for most children with persistent cough. There is need for studies to determine appropriate treatment for this persistent cough.

Abstracted from : Arch Dis Childh. 1998; Vol. 79 (5) : pp 411-414