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Prolonged post-operative course in children treated with inhaled nitric oxide for pulmonary hypertension after closure of a ventricular septal defect

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Abstract

Background and objectives: Inhaled nitric oxide (iNO) is increasingly replacing the use of hyperventilation induced alkalosis and non-selective vasodilators to treat pulmonary hypertension in the early postoperative course after congenital heart surgery. Because weaning from iNO is often difficult, complicated by a rebound phenomenon, we investigated if the presence of this phenomenon may prolong the duration of ventilatory support and the length of stay in the intensive care unit (ICU) compared to earlier treatment.

Design: Retrospective chart review.

Setting: An eight bed medical-surgical paediatric intensive care unit in a university taking care of around 150 postoperative cardiac children a year.

Patients: Comparison of two groups of children matched for age at operation, preoperative pulmonary to systemic resistance ratio, and postoperative pulmonary to systemic pressure ratio among 155 children operated on for a ventricular septum defect (VSD) associated with pulmonary hypertension (PHT) between February 1986 and January 1996, one group treated with iNO, the other without.

Measurements and results: Early postoperative morbidity was assessed using the duration of ventilatory support and length of stay in the ICU. Among 155 operated children, six patients treated with iNO and ten control patients, treated conventionally, met our matching criteria. The median length of ventilatory support for the iNO group was 6.5 (range 2-16) days and 2 (range 1-8) for the control group ($p < 0.05$). The length of stay in the ICU was 9 (range 5-23) days for the iNO group versus 4.5 (range 3-10) days for the control group ($p < 0.05$).

Conclusion: Treatment of postoperative PHT, after ventricular septal closure, with iNO is associated with a significant increase in ventilator days and length of stay in the ICU compared to earlier treatment without iNO. These findings may reflect the difficulties often encountered when weaning patients from iNO.

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Introduction

Pulmonary hypertension (PHT) remains a major cause of morbidity and mortality in the early postoperative period after repair of congenital heart defects. For a long time, deep sedation, induced alkalosis and the use of non-selective intravenous vasodilators has been the main if not exclusive modality available to reduce elevated pulmonary artery pressures. More recently, inhaled nitric oxide (iNO) has proven to be effective in severe cases[1,2] and gained popularity because of its pulmonary selectivity. However, the superiority of iNO regarding mortality and morbidity in the treatment of post-cardiac surgery PHT has never been demonstrated. Knowing that, once started, weaning of iNO can prove difficult, we questioned how this would have influenced the postoperative course. Thus, we decided to retrospectively compare the duration of ventilatory support and length of stay in the intensive care unit between two groups of children with early post-operative pulmonary hypertension following closure of a ventricular septum defect, treated, one with iNO, the other with our treatment modality before iNO was introduced.

Patients and methods

The charts of all children operated on for an isolated ventricular septal defect (VSD) who presented at pre-operative catheterization with PHT, defined as a mean pulmonary artery pressure (PAP) greater than 25 mmHg, between February 1986 and January 1996, were reviewed. According to their post-operative management, which was changed in January 1993 with the introduction of iNO, they were allocated to two groups: Group 1 when PHT had been treated with inhaled nitric oxide (iNO group) or Group 2 when PHT had been treated by ventilation induced alkalosis and non-selective vasodilators (conventional treatment group).

To allow comparison of patients with the most similar degree of pulmonary vascular lesions, a two-step patient per patient matching was performed. Patients receiving iNO were matched with patients under conventional treatment firstly by pre-operative criteria: (1) age at operation allowing an age difference of maximally 6 months, and (2) pulmonary resistance over systemic resistance ratio (Rp/Rs) accepting a difference of maximally 0.05 between the index patient and the matched patient. In a second step the following post-operative parameter was used for further matching: pulmonary artery to systemic arterial pressure ratio (PAP/SAP) within a difference of 0.05, as an index of pulmonary resistance knowing that in each case residual intracardiac shunts had been excluded by echocardiography or by calculation of Qp/Qs ratio. In the case that more than one patient from the conventional group could be matched according the outlined criteria to one index patient of the iNO group, all these patients were accepted for further analysis.

Outcome parameters were defined as the number of days of ventilatory support and the number of days in the Intensive Care Unit (ICU). Patients were discharged form the ICU 24 hours after being extubated or 24 hours after iNO was weaned in the case where iNO had been given through nasal prongs.

Post-operative management

Throughout the study period, basic post-operative management of children after closure of a VSD with PHT consisted of artificial ventilation at least to the day after the operation, continuous infusion of low-dose dopamine, sedation using nalbuphine and midazolam, and addition of positive inotropic support, mainly adrenaline when required. Mean PAP was measured by invasive monitoring with a surgically inserted small gauge catheter or evaluated by early echocardiography using the Doppler tricuspid regurgitant jet and adding the central venous pressure value. Mean systemic arterial pressure (SAP) was measured invasively with a radial or femoral catheter at all times. Extubation was always attempted as soon as haemodynamics were stable at a normal pH maintained with spontaneous ventilation.

From 1985 to 1993, elevated pulmonary artery pressure was treated with induced alkalosis by lowering $PaCO_2$, and the addition of tolazoline or nitroprussiate if judged necessary. Since 1993, iNO was introduced instead of hyperventilation and non-selective vasodilators, if the PAP/SAP ratio was greater than 50%, or if there was clinical evidence of low cardiac output (oliguria, acidosis, poor peripheral perfusion) associated with a mean PAP greater than 25 mmHg. iNO was delivered through the inspiratory limb of the respiratory circuit as described previously.[1] NO concentrations in the inspiratory limb of the ventilator circuit, were verified intermittently by chemiluminescence (CLD 700 AL, Eco Physics AG, Durnten, Switzerland). Once iNO was introduced (at 15-20 ppm) its concentration was lowered the same day to 8-12 ppm and maintained at this concentration until the next day when the first attempt to wean the patient of iNO was started. Weaning trials were repeated every 24 hours, by gradually lowering iNO-concentrations over 2-4 hours, for every patient. Weaning failure, under conditions of normoventilation or mild hyperventilation (pH between 7.40 and 7.50), was defined as a substantial increase in PAP pressures, above two-third of the value of SAP with a decrease in mean SAP and/or SaO_2. In these cases iNO was reintroduced or increased to the lowest possible concentration to maintain pre-weaning haemodynamics.

During both study periods, cardiac surgeon, surgical and anaesthetic approaches as well as overall post-operative management remained the same.

Statistical analysis

Data are given as median values (minimum, maximum). Non-parametric testing (Mann-Whitney rank sum test) was used throughout this study using Systat for Windows version 5.01 (Systat Inc., Evangston, IL). *P* values were considered to be significant if smaller than 0.05.

Results

The charts of 155 children with an isolated VSD were reviewed, of whom 86 had pre-operative catheterization. Of those, eight patients received iNO (from January 1993 to January 1996) and 78 were treated conventionally (from February 1986 to December 1992). Six patients from the iNO group could

be matched with ten patients from the conventional group according to our pre- and post-operative criteria (*Table 1*). Inhaled NO was introduced at a median time after coming of cardiopulmonary bypass of 2.5 hours (range 0-36), with 2 patients been weaned of bypass already on iNO.

The median length of ventilatory support for group 1 (iNO) was 6.5 days (range 2-16) and 2 days (range 1-8) for group 2 (conventional) ($p < 0.05$) (T*able 2*). The median length of stay in the ICU was 9 (range 5-23) days for the iNO group vs. 4.5 days (range 3-10) for the conventional group ($p < 0.05$) (*Table 2*). Intergroup analysis of repeated pH measurements, from all samples of patients on mechanical ventilation, showed no statistically significant difference between the two groups, although mean pH levels in the conventional group were slightly higher than those in the iNO group. No patient died in either group of cardiac causes.

Discussion

Our results show that children given iNO to treat early pulmonary hypertension after VSD closure required a significantly longer ventilatory support and length of stay in the ICU when compared retrospectively with, children treated with conventional treatment.

This suggests that iNO, albeit efficient, may be a questionable treatment for this condition. This conclusion obviously implies that our matching criteria allowed children with comparable degree of pulmonary vascular disease and reactivity to be equally allocated to both groups. To minimize this possible bias, we used both pre- and post-operative criteria: older age and degree of elevation of preoperative pulmonary resistance are accepted as the main factors correlating with the stage of vascular disease.[3,4] Regarding the post-operative period, pulmonary vascular resistance and reactivity can further depend on the extent of endothelial cell dysfunction related to cardiopulmonary bypass (CPB) as shown by Wessel *et al*.[5] While the mechanism of this lesion is unclear, the duration of CPB is likely to be an important factor. However, intergroup analysis comparing the length of by-pass showed no statistical difference between the two groups (*Table 2*). In our mind, the retrospective nature of the study is of less importance, in that an arbitrary choice of matching criteria would also have to be a pre-requisite for any prospective randomized study.

Attempts to explain the differences in length of ventilatory support and ICU stay between both treatments can be approached in two ways: (1) Conventional treatment favouring hyperventilation-induced alkalosis could have accelerated post-operative recovery; (2) iNO could have prolonged it. While both interventions are aimed at reducing pulmonary artery pressure, iNO acts exclusively by reducing vascular resistance and maintains cardiac output; in contrast, hyperventilation slightly decreases pulmonary vascular resistance but also increases systemic vascular resistance and reduces cardiac output.[6,7] It could be hypothesized that the decrease in pulmonary blood flow is a lesser stress for endothelial cells and hastens recovery from CPB.

However, abrupt interruption of NO delivery may result in rebound pulmonary hypertension often associated with hypoxemia and cardiovascular compromise prompting reintroduction of iNO in the clinical setting.[8] This rebound phenomenon can be explained by a feedback inhibition of NO synthase[8-10] due to an excessive amount of exogenous NO leading to a temporary deficit of endogenous NO with acute weaning. Although reversible,[11] this inhibition makes iNO weaning difficult and could explain the prolongation of intensive care observed in this study. To avoid rebound PHT, a meticulous progressive withdrawal of iNO[8] seems important. Although in our patients iNO was gradually weaned in small steps of about 1 ppm, a more progressive weaning done in very small steps of only 0.2-0.5 ppm, below a concentration of 2 ppm is now more advisable. This requires careful monitoring of the iNO at very low concentrations with a chemiluminescence method.

Others have suggested that accepting an increase in PAP for 60 minutes[12] or a fall in oxygen saturation

Table 1. Summary of patient matching

Number of patients with VSD and PHT	155	
Eliminated from study because of lack of pre-operative catheterization data	69	
Remaining patients	86	
Divided into two groups according to management:	Conventional therapy	iNO
Remaining patients (total 86)	78	8
Following matching with pre-operative data	34	7
Remaining patients after matching with post-operative data	10	6

Table 2. Population characteristics of all patients fulfilling pre- and post-operative matching criterias

	iNO (n = 6)	*Conventional treatment (n = 10)*	*Mann-Whitney*
Pre-operative variables			
Age (years)	2.05 (0.84-11.87)	2.25 (0.7-11.58)	*P* = 1
Rp/Rs	0.14 (0.1-0.27)	0.16 (0.06-0.24)	*P* = 0.745
Qp/Qs	2.8 (1.8-3.3)	3.4 (2.5-9.4)	*P* = 0.142
PAP pre-op (mmHg)	42.5 (26-70)	53.5 (26-62)	*P* = 0.744
Post-operative variables			
Pump time (minutes)	141 (80-240)	98 (85-150)	*P* = 0.277
Clamp time (minutes)	80.5 (45-103)	64.5 (42-100)	*P* = 0.278
PAP/SAP post-op (%)	59.5 (35.2-70.1)	48.8 (31.5-64.3)	*P* = 0.233
Mean pH over the first 12 hours	7.47 (7.44-7.57)	7.49 (7.42-7.56)	*P* = 0.745
Ventilation days	6.5 (2-16)	2 (1-8)	*P* = 0.021
ICU days	9 (5-23)	4.5 (3-10)	*P* = 0.018

as low as 80% over 20 minutes was sufficient to restore normal pre-rebound values.[13] We however experienced such a significant degree of cardiovascular compromise after decreasing gradually iNO that treatment had to be quickly restored. Finally, in newborns, successful weaning from iNO after withdrawal failure has been achieved by increasing briefly the inspired oxygen concentration (FiO_2).[14] Other strategies may include the use of cGMP-specific (type V) phosphodiesterase inhibitors to maintain relatively high cGMP levels at the time of weaning. Dipyridamole has been used successfully in a neonate after three unsuccessful weaning attempts[15] and more recently its effectiveness has been documented in a small number of children after repair of congenital heart disease.[16]

Although no patient died in the peri- or post-operative course, our data does not allow us to analyze mortality because of the retrospective (non-randomized) nature of the study and the limited number of patients. Moreover, only patients with an isolated VSD were included in our study. This allowed more appropriate patient matching, but may have excluded patients with higher risk of mortality and morbidity, such as patients with atrio-ventricular canal and obstructed anomalous pulmonary venous drainage

In conclusion, iNO has become an important tool in the management of pulmonary hypertension in postoperative congenital heart disease. Yet it is associated with a rebound phenomenon when abruptly withdrawn which may lead to life-threatening events necessitating reinstitution of this therapy. This may account for prolonged ventilatory support and increase in the length of stay in the ICU. To overcome this unwanted side effect, slow progressive decrease of iNO, using a standardized weaning protocol with continuous monitoring of iNO concentration is necessary. Other options such as a transient increase in FiO_2 or phosphodiesterase inhibitors seem to be promising in overcoming this rebound phenomenon but remain to be further analyzed.

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