Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study

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Summary

Background Pulmonary hypertensive crises (PHTC) are a major cause of morbidity and mortality after congenital heart surgery. Inhaled nitric oxide is frequently used as rescue therapy. We did a randomised double-blind study to investigate the role of routinely administered inhaled nitric oxide to prevent pulmonary hypertension in infants at high risk.

Methods We enrolled 124 infants (64 male, 60 female; median age 3 months [IQR 1–5]), 76% with large ventricular or atrioventricular septal defects, who had high pulmonary flow, pressure, or both, and were undergoing corrective surgery for congenital heart disease. They were randomly assigned continuous low-dose inhaled nitric oxide (n=63) or placebo (n=61) from surgery until just before extubation. We measured the numbers of PHTC, time on study gas, and hours spent in intensive care. Analysis was done by intention to treat.

Findings Compared with placebo, infants receiving inhaled nitric oxide had fewer PHTC (median four [IQR 0–12] *vs* seven [1–19]; relative risk, unadjusted 0·66, p<0·001, adjusted for dispersion 0·65, p=0·045) and shorter times until criteria for extubation were met (80 [38–121] *vs* 112 h [63–164], p=0·019). Time taken to wean infants off study gas was 35% longer in the nitric oxide group than in the placebo group (p=0·19), but the total time on the study gas was still 30 h shorter for the nitric oxide group (87 [43–125] *vs* 117 h [67–168], p=0·023). No important toxic effects arose.

Interpretation In infants at high risk of pulmonary hypertension, routine use of inhaled nitric oxide after congenital heart surgery can lessen the risk of pulmonary hypertensive crises and shorten the postoperative course, with no toxic effects.

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Introduction

Pulmonary hypertension is a major complication of surgery for congenital heart disease.[1] The hallmark of this disorder in the early postoperative period is pulmonary hypertensive crisis (PHTC), characterised by an acute rise in pulmonary vascular resistance, which initiates a cycle of right-ventricular failure and poor cardiac output. If left untreated, cardiac arrest and death may follow.[2] Despite traditional interventions, including parenterally administered vasodilators, hyperoxic hyperventilation, induced alkalosis, and inotropic support,[3] the morbidity and mortality associated with PHTC remain unacceptably high.[1]

Advances in understanding the control of vasomotor tone have highlighted the role of endothelium-derived nitric oxide as a key vasodilator substance.[4,5] Basal release of endogenous nitric oxide by the pulmonary endothelium seems to be fundamental to constant active vasodilation in this circulation.[6] Failure of nitric oxide bioavailability arises in children with congenital left-to-right shunt lesions, and this pre-existing endothelial dysfunction might be further exacerbated by congenital heart surgery.[7–9] This postoperative deficiency of pulmonary nitric oxide availability might, therefore, be pathogenically linked to PHTC.

Inhaled nitric oxide is a selective pulmonary vasodilator that acts directly on pulmonary vascular smooth muscle but has no systemic effects, since it is rapidly inactivated when exposed to haemoglobin.[10] We and others have previously reported the efficacy and safety of short-term inhaled nitric oxide in children with clinically apparent PHTC after corrective cardiac surgery.[11,12] Despite this treatment's apparent promise, complications (such as rebound pulmonary hypertension after inhaled nitric oxide being stopped[13]) have been reported. We aimed, therefore, in a prospective, randomised, double-blind, placebo-controlled trial, to study the routine use of inhaled nitric oxide after high-risk corrective congenital heart surgery and to assess its role in the prevention of pulmonary hypertension.

Methods

Patients

Eligible patients were sequentially presenting infants suitable for corrective heart sugery with high pulmonary flow, pressure, or both, congenital heart lesions, such as non-restrictive ventricular septal defect, complete atrioventricular septal defect, truncus arteriosus, or total anomalous pulmonary venous drainage, with objective evidence of pulmonary hypertension at the immediate preoperative assessment. Pulmonary hypertension was defined as a mean pulmonary artery pressure higher than 25 mm Hg or, when estimated by echocardiography, pulmonary artery pressure more than half the systemic artery pressure. When available, we used catheter-derived data rather than echo-derived data to establish eligibility. We obtained institutional ethics approval, and no eligible infant was withheld by attending clinicians. Parental consent was sought after parents had read a detailed information sheet for all eligible infants, and

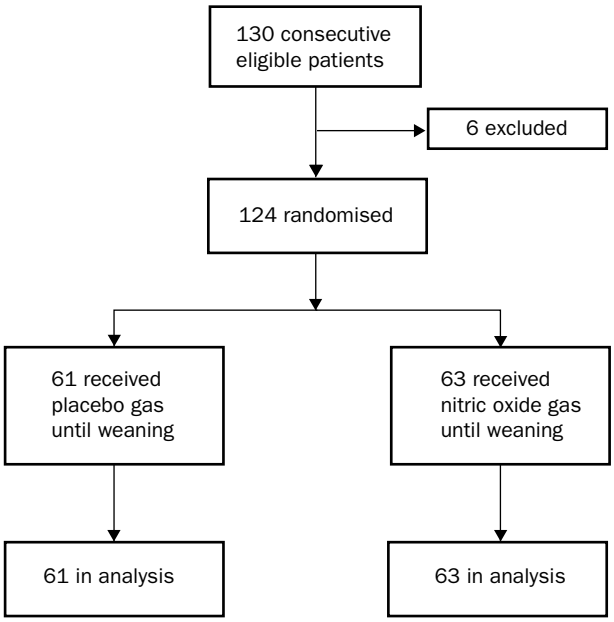

Figure 1: **Trial profile**

randomisation took place only after informed consent was obtained.

Study design

Infants were randomised locally by a computer-based stratified minimisation algorithm, based on the presence or absence of Down's syndrome (figure 1). Children with Down's syndrome may have an increased risk of pulmonary hypertension because of lung hypoplasia and obstructive airways disease in addition to the congenital heart lesion.[14] Although early surgery might reduce the postoperative risks in this syndrome,[15] we stratified infants for this disorder to ensure good balance and avoid bias in comparisons between groups. To assess the prophylactic benefit of continuous low-dose nitric oxide, randomisation was done before surgery, and inclusion in the study did not depend on postoperative haemodynamics.

Surgery and anaesthesia were done in a routine way, and a 3 French thermodilution catheter (Model 94-011-3F, Baxter Healthcare, Irvine, CA, USA) was inserted into the main pulmonary artery. The absence of any residual shunt was established by oxygen-saturation measurements from the right atrium and main pulmonary artery.

Study gas was administered continuously as inhaled nitric oxide ten parts per million or placebo nitrogen. Administration began after surgery (after chest radiography and measurement of arterial blood gas and cardiac index) until just before extubation. Other than study-gas administration, all patients were managed according to the same intensive-care protocol for sedation, ventilation, inotropes, and vasodilators (table 1). Medical grade nitric oxide at 1000 parts per million (BOC Australia, Sydney, NSW) was prepared in a base mixture of nitrogen, delivered via specially lined stainless steel cylinders and gas regulators. Medical grade nitrogen (BOC Australia) was provided in identical coded cylinders.

Study gas was delivered to the first 40 infants via a simple calibrated flow meter and mixing chamber[16] and was monitored by a commercially available electrochemical device (NOxBox, Bedfont Scientific, Upchurch, Kent, UK). All other infants received study gas via an integrated nitric oxide dosing, delivery, and analysis device (NODomo, Dräger Australia, Victoria). On the two types of nitric oxide and nitrogen dioxide monitors, the displays were masked with locked opaque covers. Based on our previous findings of similar efficacy for 2–20 parts per million inhaled nitric oxide,[12] we chose 10 parts per million to avoid any possibility of underdosing as well as potential toxic effects.[17] The maximum duration for administration of study gas was prospectively set at 7 days. Patients still ventilated at this stage were weaned from study gas and any subsequent pulmonary hypertension was treated according to our standard protocol, including the use of open-label inhaled nitric oxide (table 1).

We defined PHTC as episodes in which the pulmonary/systemic artery pressure ratio rose to more than 0·75. Episodes were classified as major if there was a fall in the systemic artery pressure of at least 20%, a fall in the transcutaneous oxygen saturation to <90%, or both, and minor if the systemic artery pressure and transcutaneous oxygen saturation remained stable.

Pulmonary artery, systemic artery, right and left atrial pressures, and transcutaneous oximetry were continuously monitored (Omnicare Component Monitoring System, Hewlett Packard, Palo Alto, CA, USA) and data were collected every minute and stored on a computerised clinical information system (Emtek/Eclipsys Corporation, Delray Beach, FL, USA).

Cardiac index, pulmonary and systemic vascular resistances were calculated by triplicate thermodilution (3 mL 0·9% saline [0–4°C]) every 12 h.

A non-clinical investigator who was aware of treatment status was available around the clock to supervise randomisation, preparation of the cylinders of study gas, and to set up gas delivery and the monitoring circuit for each patient. To avoid toxic effects, safety alarms were set at 25 parts per million for nitric oxide and 5 parts per million for nitrogen dioxide[18] and methaemoglobin concentrations were assessed twice daily. Emergency

	Routine postoperative care	Care for pulmonary hypertension with instability
Elective analgesia, sedation, and muscle relaxation	Fentanyl 2–25 μg kg^{-1} min^{-1}, midazolam 1–4 μg kg^{-1} min^{-1}, vecuronium 100–300 μg kg^{-1} h^{-1}	Bolus fentanyl (5 μg/kg)
Intermittent positive pressure ventilation	Hyperoxia (partial pressure of oxygen 13·3–20·0 kPa) hyperventilation (pH 7·4–7·5)	Partial pressure of oxygen >20 kPa pH >7·50
Vasopressors	Dopamine 3–5 μg kg^{-1} min^{-1}, epinephrine 0·05–2·0 μg kg^{-1} min^{-1}, norepinephrine 0·05–2·0 μg kg^{-1} min^{-1}	Increase vasopressors as required
Vasodilators	Glyceryl trinitrate 1–4 μg kg^{-1} min^{-1}, sodium nitroprusside 1–4 μg kg^{-1} min^{-1}	Increase vasodilators as required, epoprostenol (5–25 ng kg^{-1} min^{-1})
Other	Cautious tracheal suction: preoxygenate, premedicate fentanyl, study gas (for trial patients)	If still unstable, add open-label inhaled nitric oxide (10 ppm)

ppm=parts per million.

Table 1: **Protocol for management of patients at risk of or with pulmonary hypertension**

	Nitric oxide (n=63)	Placebo (n=61)
Demography		
Sex (male/female)	36/27	28/33
Median (IQR) age (months)	3 (1–5)	2 (1–4)
Down's syndrome	24	21
Diagnosis		
Ventricular septal defect	29 (46%)	19 (31%)
Atrioventricular septal defect	18 (29%)	18 (30%)
Truncus arteriosus	8 (13%)	13 (21%)
Total anomalous pulmonary venous drainage	6 (9%)	11 (18%)
Other	2 (3%)	0
Haemodynamics (median [IQR])		
Pulmonary artery pressure (mm Hg)	20 (17–22)	20 (18–25)
Systemic artery pressure (mm Hg)	66 (59–72)	60 (54–71)
Pulmonary vascular resistance index (dynes s $cm^{5\ -1}\ m^{2\ -1}$)	212 (159–253)	223 (182–398)
Systemic vascular resistance index (dynes s $cm^{-5}\ m^{-2}$)	1181 (1014–1349)	1272 (950–1510)

There were no significant differences between groups in any of these characteristics.

Table 2: **Baseline characteristics**

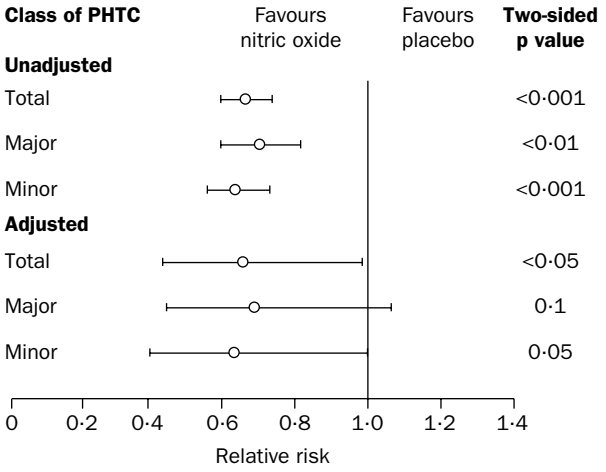

Figure 2: **Relative risk (95% CI) of PHTC in nitric oxide compared with placebo group**

protocols for the management of gas alarms or clinically important methaemoglobinaemia (>5%) were kept at each infant's bedside.

Chest radiographs were taken soon after surgery (day 0) and on days 3 and 7. The latter radiographs were reviewed independently by a chest physician and radiologist who were unaware of study-gas assignment, and given a predefined lung injury score (0 normal, 1 involvement of one lobe, 2 involvement of two lobes, 3 involvement of >2 lobes or one lung, 4 bilateral widespread opacities). A safety monitoring committee reviewed the indicators for toxic effects and chest radiographs after every ten infants were recruited.

A standard protocol was followed for prevention and treatment of clinically important pulmonary hypertension. If pulmonary hypertension was clinically important (pulmonary/systemic artery pressure ratio >0·50, together with haemodynamic instability, or >0·75 at any time), medical treatment was intensified in stepwise fashion (table 1). Pulmonary hypertension without instability did not prompt a change in the normal management protocol. Persistent or recurrent major PHTC, associated with clinical deterioration unresponsive to the maximum conventional treatment, was the criterion for the introduction of open-label inhaled nitric oxide (10 parts per million) as rescue gas in addition to study gas. The duration of rescue therapy was decided by the attending physician.

Treatment was withdrawn in a consistent sequential way by allowing the arterial carbon dioxide tension to normalise under heavy sedation, muscle relaxation, and inotropic support. If no PHTC ensued, muscle relaxation was stopped, sedation was reduced, and the infant was weaned off mechanical ventilation in accordance with normal intensive-care practice.

Predefined extubation criteria were: haemodynamic stability (an absence of major PHTC during the previous 6 h, hourly urine output >0·5 mL/kg, no acidosis, mean systemic artery pressure within age-related normal values); and satisfactory gas exchange (partial pressure of carbon dioxide <6·0 kPa, and of oxygen >13·3 kPa, and spontaneously breathing an inspired oxygen fraction <0·40 at a mechanical ventilation rate of <8 breaths per min).

When infants were eligible for extubation, the non-clinical investigator reduced the study-gas flow by 20% per h, aiming for complete withdrawal after 4 h. The study-gas flow rate was masked at all times from attending clinicians. If major PHTC occurred, the weaning process was suspended, initially for 1 h. Instability after three successive attempts at any stage led to a 12 h pause. Clinicians were free to use optimum cardiorespiratory support during weaning from study gas. The primary endpoint was the reduction of PHTC. The main secondary endpoint was reduction in the time to eligibility for extubation.

Statistical analysis

We sought a 50% decrease in the number of PHTC with nitric oxide. The absolute incidence of postoperative PHTC in infants at high risk has not been well documented. Unpublished data from our unit together with published reports[1] suggest that up to 50% of at-risk children might suffer at least one postoperative PHTC, and our pilot data suggest a mean of 2·8 (SD 2·9) episodes per patient in the postoperative period.

For the effect of treatment on the time until the objective criteria for extubation were met, previous experience suggested that the average time to extubation was about 6 days (3·4).[13] We required a 30% reduction (about 2 days) in the time to reach the criteria for weaning. To detect these reductions with 80% power at a two-sided significance of 0·05, we needed to recruit 136 and 112 infants for these study endpoints, respectively.

We compared baseline characteristics between groups with unpaired Student's *t* tests (or Wilcoxon's rank sum tests for non-normal data), with Bonferroni correction for

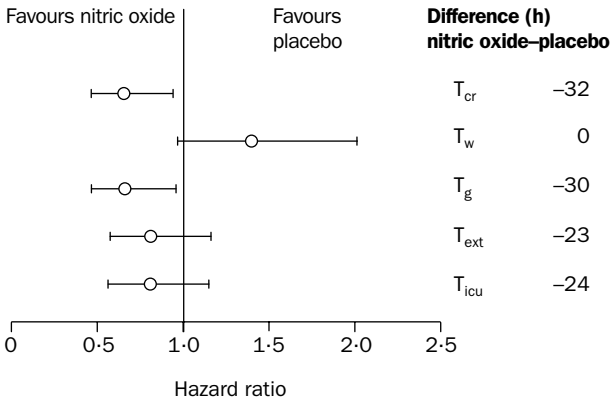

Figure 3: **Hazard ratios (95% CI) for postoperative course with differences in median times.**

T_{cr}=time to criteria for weaning; T_w=time weaning; T_g=time on study gas; T_{ext}=time to extubation; T_{icu}=time in intensive-care unit.

multiple comparisons. All analyses were done by intention to treat. Since the data were unlikely to be normally distributed, we analysed the outcomes based on time to reach set criteria with survival-time methods based on the log-rank test. The counts over time of the numbers of PHTC were analysed by Poisson regression. If the variance substantially exceeded the mean count, the Poisson regression was adjusted for overdispersion; we present adjusted and unadjusted analyses. For subsidiary analyses of normally distributed data, means (SD) are presented and differences between groups assessed with unpaired *t* tests. For data not normally distributed, medians (IQR) are shown and non-parametric methods were used. Additional analyses for outcomes related to time were done with Cox's proportional hazards regression, with adjustment for baseline characteristics. We took $p<0·05$ to be significant. Interim analyses were scheduled when recruitment reached 100 randomised infants, and final analyses were done when all 124 randomised infants had completed the study.

Results

124 (95%) of 130 eligible infants were randomised at the start of surgery; the other six were excluded because parental consent could not be obtained. Baseline characteristics were similar for the two groups (table 2).

Infants who received inhaled nitric oxide had significantly fewer PHTC than those receiving placebo (median four [IQR 0–12] *vs* seven [1–19]; unadjusted relative risk 0·66 [95%CI 0·59–0·74] $p<0·001$; adjusted for dispersion 0·65 [0·43–0·99], $p=0·045$; figure 2).

The median time to eligibility for extubation was shorter in the inhaled nitric oxide group than in the placebo group (80 [38–121] *vs* 112 h [63–164]; $p=0·019$) and the median weaning time from study gas was similar in the two groups (4 [4–5] *vs* 4 h [4–4], hazard ratio 1·35; $p=0·19$). In the inhaled nitric oxide group, 17 infants required longer than 4 h for weaning, compared with two in the placebo group. Despite a longer weaning time, the total time on study gas, including weaning time, was still shorter in the nitric oxide group than in the placebo group (87 [43–125] *vs* 117 h [67–168], $p=0·023$; figure 3)

The pulmonary vascular resistance index, measured every 12 h, did not differ between groups at baseline but was significantly lower during study-gas administration compared with the placebo group ($p<0·001$, figure 4).

During the study period, seven (6%) infants, two from the active treatment group and five from the placebo group, required rescue inhaled nitric oxide. The duration of rescue nitric oxide was similar for the two groups.

102 (82%) infants completed the study in less than 7 days; the remainder (n=22) were weaned from the study gas at 7 days as per protocol. Significantly fewer patients in the inhaled nitric oxide group were still ventilated at 7 days than in the placebo (six [10%] *vs* 16 [26%], $p=0·02$).

After weaning from study gas, a similar proportion of infants in each group had an extubation delay of more than 6 h (nitric oxide 55, placebo 53). The median time intubated was shorter in the nitric oxide than in the placebo groups (117 [70–173] *vs* 140 h [86–214]), as was the median time to discharge from intensive care (138 [89–192] *vs* 162 h [96–222]), but these differences were not significant.

There were eight deaths (6·5% of whole study group, five on nitric oxide, three on placebo; $p=0·49$), 11 h to 42 days after surgery. This overall death rate is the same or less than that reported by other major centres for similar groups of high-risk young infants who underwent

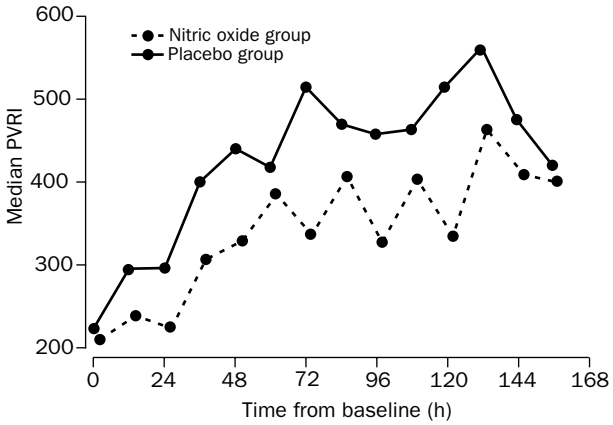

Figure 4: **Median pulmonary vascular resistance index by treatment group over time after surgery until eligible for extubation**

surgery for congenital heart disease.[19,20] Only one patient died while still in the study protocol (≤7 postoperative days). This patient, with truncus arteriosus and interruption of the aortic arch, died from surgical complications in the immediate postoperative period. Two patients died from low cardiac output (one after reoperation for mitral-valve replacement) and three died from sepsis. None of the six deaths was related to pulmonary hypertension. Only two patients (one in each group) died from suspected PHTC, each associated with pneumothorax, at 192 h and 222 h, respectively, after surgery. Thus none of the eight deaths seemed related to the effects of study gas.

Methaemoglobin or nitrogen dioxide levels were never judged to have reached toxic levels; the maximum methaemoglobin recording was 3·4% and the maximum nitrogen dioxide level in any infant was 2·1 parts per million. Furthermore, the mean methaemoglobin concentrations for each group at any time during the study did not differ significantly. Most patients had no radiographic evidence of lung injury. The proportion of infants with a lung injury score of less than 1 was 82%, 59%, and 72% on days 0, 3, and 7, respectively. There were no differences between the treatment groups in lung injury scores on any day.

Discussion

Congenital heart disease is present in five to ten per 1000 livebirths.[21] If surgery is required, the most common lesions (such as ventricular septal defect and atrioventricular septal defect) are characterised by raised pulmonary blood flow, pulmonary artery pressure, or both, which result in a high risk of potentially life-threatening postoperative PHTC.[22]

Children with high pulmonary flow, pressure, or both have impaired endothelium-dependent vasodilatation in the pulmonary circulation, which might be exacerbated by cardiopulmonary bypass.[7,8,23] As a result, the bioavailability of the endothelium-derived vasodilator nitric oxide seems deficient, and predisposes individuals to pulmonary vasoconstriction and hypertension in the postoperative period. In support of this notion, postoperative pulmonary hypertension in these children can be acutely improved by the administration of exogenous inhaled nitric oxide or by stimulation of endogenous release of nitric oxide with L-arginine (the substrate for nitric oxide) or substance P infusion.[9]

We found that inhaled nitric oxide was safe, consistently lowered pulmonary vascular resistance,

resulted in at least a 30% lower frequency of PHTC, shortened the time to eligibility for extubation, lowered the risk of long-term intubation, and did not lead to clinically important rebound pulmonary hypertension. Although previous non-randomised studies have supported the use of inhaled nitric oxide as rescue therapy for pulmonary hypertension after surgery for congenital heart disease,[11] and some randomised work has confirmed a reduction in pulmonary artery pressure with short-term inhaled nitric oxide in the operating room,[24] our data suggest that routine continuous inhaled nitric oxide therapy in at-risk children is of further clinical benefit.

In addition to the benefits of a lowered frequency of PHTC and a reduced requirement for long-term ventilation, the overall time to eligibility for extubation was significantly shorter, by about 30 h, in the children receiving inhaled nitric oxide than in those receiving placebo. Although the time to wean infants off study gas was non-significantly increased (by about 35%) in the inhaled nitric oxide group, the process was successful in most cases because of a protocol for gradual withdrawal over at least 4 h. Strategies to manage rebound pulmonary hypertension included transient intensification of oxygen delivery, mechanical ventilation, vasodilator treatment, or a combination of these when clinically necessary. Since the trial protocol was implemented, alternative strategies to avoid rebound pulmonary hypertension have been reported.[25,26] Despite an increased weaning time, the total time on study gas (ie, time to extubation criteria plus hours required for weaning) was also significantly shortened by more than 24 h, even after adjustment for age, diagnosis, and the presence of Down's syndrome.

By contrast however, the actual time ventilated and length of stay in intensive care were not significantly different in the two groups, although these times were shorter by about 24 h in the nitric oxide group than in the placebo group. Although clinically important, these endpoints were thought to be less reliable than the objectively measured criteria for extubation eligibility, since various non-treatment-related factors contributed to the time from successful withdrawal of study gas to actual extubation. These factors included removal of transthoracic lines, time of day, number of staff on wards and in intensive care, and availability of non-intensive-care beds.

Early reports on the use of inhaled nitric oxide as rescue therapy for established pulmonary hypertension focused on primary pulmonary hypertension in adults,[27] persistent pulmonary hypertension in neonates[28] and adult respiratory distress syndrome.[29] Randomised trials have not yet been done for inhaled nitric oxide in primary pulmonary hypertension. In neonates with pulmonary hypertension, large-scale studies have supported the routine use of inhaled nitric oxide to lower morbidity and limit invasive treament, although no substantial reduction in mortality has been shown.[30] By contrast, studies in children and adults with respiratory distress syndrome have shown no clinical benefit from routine use.[31,32] It cannot be presumed, therefore, that short-term efficacy in the presence of established pulmonary hypertension or lung injury will translate into benefit from routine prophylactic use of inhaled nitric oxide in high-risk patients.

Although we showed a reduction in postoperative morbidity with nitric oxide in children with pulmonary hypertension, mortality was not affected. Only one of the eight deaths occurred during the study-gas administration and was attributable to a surgical complication unrelated to the study treatment. The other seven deaths occurred when infants were no longer under the study protocol, and were mainly related to low cardiac output and septicaemia, disorders not previously associated with inhaled nitric oxide. In vitro, nitric oxide has a bacteriostatic influence on certain pathogens,[33] but whether this effect is beneficial has not been clear during treatment with inhaled nitric oxide in vivo. Although systemic nitric oxide might influence immune function, inhaled nitric oxide is completely inactivated on absorption into the pulmonary capillary bed and, therefore, should not influence the risk of infection.

The lack of a significant mortality difference between groups might have been due partly to the rapid detection and treatment of PHTC with non-nitric oxide measures, and the prompt use of rescue inhaled nitric oxide if those treatments failed. A much larger number of patients would be required to investigate mortality outcomes reliably, given the relatively low incidence of death in this (6·5%) and similar cohorts.

Furthermore, although the frequency of PHTC was significantly reduced by the use of inhaled nitric oxide, such crises were not abolished. This may have been due to an insufficient dose of inhaled nitric oxide, although we have shown previously that doses as low as 2 parts per million are sufficient to reverse acute pulmonary hypertensive crises.[12] This observation suggests that important pathogenic mechanisms in addition to a relative deficiency of nitric oxide in the pulmonary circulation are involved in postoperative pulmonary hypertension. Nevertheless, the clinical implication is that routine prophylactic use of inhaled nitric oxide at 10 parts per million will reduce the frequency of major pulmonary hypertensive crises and lessen time to extubation eligibility by 1 day or more. The routine use of inhaled nitric oxide in intensive care was uncomplicated, easy for staff to understand and monitor, and the weaning protocols could be carried out without difficulty.

Since nitric oxide treatment is simple, safe, and effective, its routine clinical use may be justified in such patients.

Contributors

Owen Miller, the chief investigator, wrote the trial protocol and grant and ethics submissions, supervised the trial day to day, and drafted the paper. David Celermajer and Anthony Keech were involved in the trial design, ongoing review, and data interpretation, and in the preparation of the final paper. Swee Fong Tang and Nicholas Pigott, research fellows, were involved in recruitment of patients, trial coordination, clinical supervision, emergency availability, review of the paper, and final approval. Elaine Beller contributed to the design of the study protocol, randomisation program, and database; statistical analysis, review of the paper, and final approval.

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