# Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants

N V Subhedar, S W Ryan, N J Shaw

**Abstract**

***Aim*—To determine whether treatment with inhaled nitric oxide (NO) and/or dexamethasone reduces the incidence of chronic lung disease (CLD) and/or death in high risk preterm infants.**

***Methods*—Infants below 32 weeks of gestation were recruited at 96 hours of age if they were deemed to be at high risk of developing CLD. Infants were randomly assigned to one of four treatment groups using a factorial design: (1) 5–20 parts per million inhaled NO for 72 hours; (2) 0.5–1 mg/kg/day intravenous dexamethasone for 6 days; (3) both drugs together; (4) continued conventional management.**

***Results*—Forty two infants were randomised: 10 infants received inhaled NO alone; 11 dexamethasone alone; 10 both treatments; and 11 neither treatment. There was no difference in the combined incidence of CLD and/or death before discharge from hospital between either infants treated with inhaled NO and controls (RR 1.05, 95% CI 0.84–1.25), or those treated with dexamethasone and controls (RR 0.95, 95% CI 0.79–1.18).**

***Conclusions*—At 96 hours of age, neither treatment with inhaled NO nor dexamethasone prevented CLD or death.**

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Keywords: randomised controlled trial; nitric oxide; dexamethasone; chronic lung disease

Antenatal corticosteroids and postnatal surfactant treatment reduce neonatal mortality in preterm infants. However, in recent years the incidence of chronic lung disease of prematurity (CLD) has increased which is only partly explained by the greater survival of extremely low birthweight infants.[1] Chronic lung disease remains one of the most important consequences of neonatal intensive care.

Interventions aimed at preventing pulmonary damage through a reduction in ventilator and oxygen induced injury, or through a modification of the resulting inflammatory process, may help to prevent the development of CLD in immature lungs. Inhaled nitric oxide (NO) and early corticosteroid treatment have both been proposed as potentially beneficial treatments in respiratory distress syndrome (RDS).[2–4]

Raised pulmonary vascular resistance and ventilation–perfusion mismatch are important features in the pathophysiology of RDS. Inhaled nitric oxide may have a therapeutic role through its selective pulmonary vasodilator effects.[5] The use of inhaled NO in preterm infants is now becoming widespread despite the absence of published controlled data of its efficacy and concerns about its safety.

Postnatal corticosteroids aid successful extubation and shorten the duration of mechanical ventilation in infants with RDS after the first week of life. Unfortunately there is little evidence of benefit from corticosteroids in longer term studies of outcome.[6] Studies of earlier treatment with steroids in RDS, in an attempt to interrupt the progression of the disease process and minimise pulmonary damage, have produced conflicting results.[3 4 7 8]

Having produced and validated a scoring system for predicting infants at high risk,[9] we aimed to investigate the efficacy and safety of treatment with early intravenous dexamethasone and/or inhaled NO in preterm infants.

## Methods

Preterm infants admitted to the neonatal intensive care unit at Liverpool Women's Hospital were studied between the beginning of August 1995 and the end of September 1996. The study was an open, randomised controlled trial using a factorial design, and was approved by the local paediatric ethics committee.

Infants were eligible for entry into the trial at 96 hours of age if they met the following criteria: (1) gestational age < 32 weeks completed weeks; (2) mechanically ventilated since birth for respiratory distress; (3) received surfactant therapy; and (4) deemed to be at high risk of developing CLD as defined by a modified CLD prediction score.[9] Exclusion criteria included major congenital anomaly, structural cardiac defect or significant ductal shunting, culture positive sepsis, intraventricular haemorrhage (IVH) with parenchymal involvement, and pulmonary or gastrointestinal haemorrhage. Infants with disordered coagulation or thrombocytopenia (platelets < 50), were also excluded. Parental consent was sought as soon as possible once the infant had met the entry criteria. Infants were randomised into one of four treatment groups: (1) inhaled nitric oxide (group 1); (2) intravenous dexamethasone (group 2); (3) both treatments together (group 3); and (4) no new treatment (group 4). Block randomisation was performed using computer generated random numbers and sealed envelopes.

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Demographic data were collected from maternal and infant case notes. Assessment of gestational age was made from maternal dates and/or an early ultrasound scan. Other details collected included place of birth, mode of delivery, any treatment with antenatal corticosteroids, multiple pregnancy, Apgar scores, birthweight and sex.

Following initial intubation and stabilisation in the delivery room, all infants with early onset respiratory distress received two doses of artificial surfactant (ALEC, Britannia Pharmaceuticals), on admission to the unit and again at 12 hours of age. Those below 1 kg were also treated with prophylactic indomethacin, 0.1 mg/kg/dose at intervals of 12 hours, immediately after birth and for two further doses. Respiratory support was provided with time cycled, pressure limited mechanical ventilators (SLE 2000) in all cases. Weaning from mechanical ventilation followed a consistent pattern, with an initial reduction in peak inspiratory pressure to 12 cm $H_2O$ and a subsequent reduction in respiratory rate. Extubation into head box oxygen was performed directly from a low ventilator rate (5–10 breaths per minute). All infants received intravenous aminophylline during the weaning process. Ventilatory support and inspired oxygen concentration ($FIO_2$) were adjusted to maintain arterial blood gases within a range where pH was 7.30–7.45, $PaO_2$ 50–80 mm Hg, and $PaCO_2$ 40–50 mm Hg. Plasma glucose concentrations were measured concurrently with blood gas analysis. All infants continued to receive supplemental oxygen until arterial oxygen saturations were consistently above 93%.

## Treatment dose and monitoring regimens

### NITRIC OXIDE

Nitric oxide was supplied in a concentration of 1000 parts per million (ppm) in a balance of nitrogen, with a certified residual nitrogen dioxide ($NO_2$) concentration of < 0.2% (BOC special gases). The gas was administered into the inspiratory limb of the ventilator circuit, distal to the humidifier, and continuous monitoring of inhaled NO concentration was performed close to the endotracheal tube, allowing 20 cm for adequate mixing of inhaled gases. Nitrogen dioxide concentrations were monitored intermittently at the same point at 1 and 2 hours following onset of treatment, and at 4 hourly intervals thereafter. Monitoring of inhaled NO and $NO_2$ was performed using electrochemical sensors (Microgas MG2000, Micro Medical). Methaemoglobin concentrations were measured (IL 482 co-oximeter, Instrumentation Laboratory) at 1 and 4 hours, and 12 hourly thereafter. Scavenging was performed using a soda lime canister (Sofnolime, Molecular Products) placed in the expiratory limb of the ventilator circuit.

Inhaled nitric oxide was started at a dose of 20 ppm and weaned according to the response achieved within the first 2 hours of treatment. A "positive" response in oxygenation was inferred if there had been a decrease in oxygenation index (OI; $FIO_2 \times$ mean airway pressure $\times$ 100/ $PaO_2$) by 25% or more, or a reduction in the $FIO_2$ of 0.10 or more in infants without arterial access. At 2 hours, if a response had been observed, the dose of inhaled NO was weaned by 5 ppm. If tolerated, weaning was continued in steps of 5 ppm every 15 minutes to a minimum dose of 5 ppm which was continued for 72 hours. A deterioration at any time during the weaning process (an increase in OI by 25%, or $FIO_2$ by 0.10) was an indication to return to, and remain at, the previous effective dose. After 72 hours of continuous treatment an attempt was made to wean and/or stop inhaled NO. If unsuccessful, further attempts to wean treatment were made at 24 hour intervals thereafter.

Although medical and nursing staff were aware of the treatment being administered, decisions regarding inhaled NO treatment dose were taken independently. Nitric oxide inhalation was stopped if haemorrhagic complications occurred (cerebral parenchymal, pulmonary, or gastrointestinal) or if clinically relevant ductal shunting developed at any time.

### DEXAMETHASONE

Intravenous dexamethasone was given at 12 hourly intervals for 6 days in total; 0.5 mg/kg/dose for six doses, and 0.25 mg/kg/dose for a further six doses. The dose of dexamethasone was reduced if hypertension (defined as mean arterial pressure greater than 2 standard deviations from the mean for age) or hyperglycaemia (defined as a plasma glucose concentration requiring a reduction in the intake of intravenous glucose) occurred and were resistant to treatment. Sepsis with positive blood or cerebrospinal fluid cultures unresponsive to antibiotic treatment, and gastrointestinal haemorrhage or perforation, were indications for stopping dexamethasone. Ranitidine was administered for minor gastrointestinal bleeding associated with treatment. During the course of the study it was reported by the independent data assessor that gastrointestinal side effects associated with dexamethasone were unacceptably high. The starting dose was therefore reduced to 0.5 mg/kg/day. Only three infants received this reduced dosage regimen before the study was terminated.

The primary outcome of interest in this study was the combined incidence of death before discharge and CLD. Chronic lung disease was defined as continuing oxygen dependency for at least 28 days and beyond 36 weeks postmenstrual age, with an abnormal chest radiograph appearance.[10] Secondary outcomes included time to successful extubation (extubation for >24 hours), duration of mechanical ventilation, length of hospital stay, and incidence of neonatal complications such as air leak, patent ductus arteriosus (PDA) requiring medical or surgical intervention, necrotising enterocolitis (NEC), IVH, and culture positive sepsis (within the neonatal period). Potential side effects of each treatment were also monitored and recorded.

Two dimensional and Doppler echocardiography were performed to exclude structural cardiac defects and evaluate ductal patency

*Table 1 Patient characteristics*

| | *Nitric oxide* | | *Dexamethasone* | |
|---|---|---|---|---|
| | *Treatment (n=20)* | *Controls (n=22)* | *Treatment (n=21)* | *Controls (n=21)* |
| Birthweight (g)* | 882 (416-1354) | 750 (520-1400) | 870 (530-1400) | 818 (520-1222) |
| Gestational age (weeks)* | 27 (24-30) | 27 (22-31) | 27 (22-31) | 27 (22-31) |
| Sex (M:F) | 12:8 | 5:17 | 7:14 | 10:11 |
| Multiple pregnancy | 7 (35%) | 6 (27%) | 6 (29%) | 7 (33%) |
| Antenatal steroids | 16 (80%) | 18 (82%) | 17 (81%) | 17 (81%) |
| Caesarean section | 15 (75%) | 11 (50%) | 14 (67%) | 12 (57%) |
| Outborn | 6 (30%) | 7 (32%) | 7 (33%) | 6 (29%) |
| Apgar score (5 min)* | 8 (2-10) | 8 (3-10) | 8 (3-10) | 8 (2-10) |

* Values expressed as median (range).

and haemodynamics before trial entry, and daily for the first week after treatment (Vingmed CFM 725, Sonotron or ATL Ultramark IV, Advanced Technical Laboratories). Information from the echocardiographic examination was made available only if a clinically important PDA was suspected by the medical staff. Clinically important left to right ductal shunting through a PDA (left atrial to aortic root ratio >1.5)[11] was treated with indomethacin 0.1 mg/kg/d for six days. Ligation was performed if there had been an inadequate response to two courses of indomethacin.

Cranial ultrasound scans were performed as a baseline, at weekly intervals for the first month, and again before discharge as a minimum. Infants with IVH were scanned more frequently to document evolving lesions. Scans were reported by the attending medical staff and classified as grades 1 to 3.[12] NEC was diagnosed in the presence of characteristic clinical features (abdominal distension and gastrointestinal haemorrhage) with intramural gas on radiography, or on macroscopic or histological findings at laparotomy or post mortem examination. Screening for retinopathy of prematurity (ROP) was performed by a paediatric ophthalmologist and graded according to the international classification.[13]

### STATISTICAL ANALYSIS

The factorial design of the study led produced two treatment groups and two control groups. Infants treated with inhaled NO (groups 1 and 3) were compared with control infants who did not receive inhaled NO (groups 2 and 4). Infants treated with dexamethasone (groups 2 and 3) were compared with controls who did not receive dexamethasone (groups 1 and 4). The nature of the study also enabled a further comparison to be made of the combined effect of both treatments (group 3) against controls receiving neither treatment (group 4).

Initial calculations suggested that a sample size of 88 infants would be needed to demonstrate a reduction in the incidence of CLD/death from 75% to 40% at the 2.5% significance level (to allow for a Bonferroni correction for comparisons between two treatment groups), with a power of 80%. It was planned that an interim analysis would be performed by an independent data assessor at the estimated mid-point of the trial, after 12 months of recruitment. The purpose of this analysis was to detect any obvious excess of important adverse effects in either treatment group and to allow a re-evaluation of the estimated sample size based on the incidence of the primary outcome during the first 12 months of recruitment. The interim analysis revealed the incidence of CLD/death in the control groups to be much greater than initially predicted (97–100% instead of 75%). This would have enabled the proposed effect to be detected with a much smaller study group. Additionally, further recruitment would have been highly unlikely to demonstrate any significant benefit from either treatment. The study was therefore terminated on the advice of the data assessor after 14 months of recruitment.

Outcome variables were analysed on an intention to treat basis, with all randomised infants included in the final analysis. Differences between treatment groups were compared using the Mann-Whitney U test for continuous variables, and $\chi^2$ test, or Fisher's exact test for categorical variables. Results are presented as median (range) and differences between primary outcomes expressed as relative risks with 95% confidence intervals. Tabulated results are presented as groups of treated infants compared with their respective controls, as described above. Data were analysed using SPSS statistical software (SPSS release 4.0).

*Table 2 Secondary outcome measures*

| | *Nitric oxide* | | *Dexamethasone* | |
|---|---|---|---|---|
| | *Treatment* | *Controls* | *Treatment* | *Controls* |
| Duration of ventilation (days)* | 11 (5-44) | 19 (5-39) | 23 (6-44) | 13 (5-39) |
| Time to extubation (days)* | 6.5 (5-28) | 11 (5-35) | 8.5 (5-35) | 11 (5-28) |
| Duration of hospitalisation (days)* | 97 (74-112) | 96 (63-142) | 100 (63-142) | 95 (69-125) |
| Maximum grade of IVH* | 2 (0-2) | 2 (0-3) | 2 (0-3) | 1 (0-3) |
| Pulmonary haemorrhage | 2 (10%) | 2 (10%) | 2 (10%) | 2 (10%) |
| Pneumothorax | 3 (15%) | 1 (5%) | 3 (14%) | 1 (5%) |
| Symptomatic PDA | 4 (20%) | 3 (15%) | 3 (14%) | 4 (19%) |
| Indomethacin | 3 (15%) | 1 (5%) | 1 (5%) | 2 (10%) |
| Ligation | 1 (5%) | 2 (10%) | 2 (10%) | 2 (10%) |
| Necrotising enterocolitis | 1 (5%) | 2 (10%) | 2 (10%) | 1 (5%) |
| Stage 3/4 ROP | 2 (10%) | 0 | 2 (10%) | 0 |
| Episodes of neonatal sepsis* | 1 (0-3) | 1 (0-4) | 1 (0-3) | 1 (0-4) |

* Values expressed as median (range).
ROP = retinopathy of prematurity.

## Results

During the period of study 63 infants were eligible to take part. Twenty one were excluded before randomisation: 11 had evidence of severe intraventricular or pulmonary haemorrhage, three had structural cardiac defects, and

in seven infants consent was not obtained for study. Forty two infants were randomised, all of whom received treatment in the appropriate group and were followed up successfully. Ten infants received inhaled NO alone, 11 dexamethasone alone, 10 both treatments and 11 neither treatment. Seventeen infants died before discharge from hospital. The principal causes of death were: severe RDS in 13 infants; bronchopulmonary dysplasia in two; and septicaemia in two.

Patient characteristics are shown in table 1. Paired groups were broadly comparable, although infants in both treatment groups were heavier than control infants and there was a higher proportion of boys in the inhaled NO treatment group.

### TREATMENT WITH INHALED NITRIC OXIDE

Seven infants completed the full course of treatment: of the remainder, four died and seven were extubated within 72 hours of treatment. Inhaled nitric oxide was also withdrawn in one infant who developed major left to right ductal shunting and in another who had a pulmonary haemorrhage. However, these events (which may be considered possible complications of inhaled NO therapy) did not occur more frequently overall in treated infants when compared with controls (table 2). No infant treated with inhaled NO sustained a progression or extension of an existing IVH.

Intra-arterial monitoring was performed in 19 treated and 16 control infants at entry into the study. Mean airway pressure (MAP), maximum peak inspiratory pressure (PIP) in the first 96 hours, $FIO_2$ and oxygen index (OI) were all higher in infants treated with nitric oxide compared with controls (table 3). The overall CLD risk score was, however, similar in the two groups probably reflecting the lower median birthweight of control infants.

The median dose of inhaled NO administered within the initial 72 hour period was 5 ppm (range 5–20 ppm). One infant required reduction of the dose of inhaled NO because of high $NO_2$ concentrations (2.5–3 ppm). In all other infants concentrations of $NO_2$ remained below 2 ppm. Methaemoglobin concentrations were below 3% in all infants. Treatment was successfully withdrawn in all seven infants who completed 72 hours of inhaled treatment, despite a small increase in oxygen requirement after inhaled NO had been stopped.

The primary outcome measure of the combined incidence of death and CLD was similar in both groups (table 4). There was a greater number of deaths in infants treated with inhaled NO compared with controls (10 *vs* 7, respectively), although this difference was not significant. All surviving infants in the treatment group, and all except one survivor from the control group, subsequently developed CLD. There were no significant differences between treated and control infants in any of the secondary outcome measures shown in table 2.

### TREATMENT WITH DEXAMETHASONE

Baseline characteristics were similar in the two groups (table 3). However, infants treated with dexamethasone tended to have more severe respiratory disease. This was reflected by greater respiratory support and a higher median OI compared with control infants.

Twelve infants completed treatment with 12 doses of dexamethasone. Five of the nine remaining infants died within the treatment period, and dexamethasone was stopped in a further four infants following the development of extensive gastrointestinal complications (ileal perforation in two infants, and abdominal distension with upper gastrointestinal haemorrhage in two infants). Two infants in the control group also developed gastrointestinal complications, including one with an isolated ileal perforation. Hyperglycaemia was seen more commonly in the control group, six of 21 compared with three of 21 in infants treated with dexamethasone ($p = 0.45$). One treated infant received insulin for hyperglycaemia. No infant in either group received intervention for hypertension. Although the overall incidence of sepsis in the neonatal period was similar in both groups, two infants developed *Pseudomonas* septicaemia during their course of treatment with dexamethasone. In all other cases of culture confirmed sepsis the organism isolated was coagulase negative *Staphylococcus*.

None of the differences between primary or secondary outcome measures was significant (tables 2 and 4). In particular, the combined incidence of death and CLD was similar in both groups. The only surviving infant without CLD belonged to the dexamethasone treatment group.

*Table 3 Baseline parameters*

| | *Nitric oxide* | | *Dexamethasone* | |
|---|---|---|---|---|
| | *Treatment* | *Controls* | *Treatment* | *Controls* |
| CLD risk score* | 0.77 (0.43-1.0) | 0.79 (0.27-0.98) | 0.75 (0.43-1.0) | 0.80 (0.27-1.0) |
| MAP* | 9 (4-21) | 7 (3-12) | 8 (3-21) | 8 (4-18) |
| Maximum PIP* | 28 (16-42) | 24 (16-38) | 28 (16-42) | 26 (16-40) |
| $FIO_2$* | 0.45 (0.22-1.0) | 0.37 (0.21-0.72) | 0.4 (0.21-1.0) | 0.36 (0.21-0.84) |
| Oxygenation index* | 7.9 (1.6-46.7) | 3.9 (1.2-11.5) | 7.9 (1.2-46.7) | 4.1 (1.4-28) |
| PDA | 5 (25%) | 4 (19%) | 3 (14%) | 5 (24%) |
| Pneumothorax | 5 (25%) | 3 (14%) | 5 (24%) | 3 (14%) |
| IVH grade | | | | |
| 1 | 3 (15%) | 1 (5%) | 2 (10%) | 2 (10%) |
| 2 | 9 (45%) | 10 (45%) | 12 (57%) | 7 (33%) |
| Trial entry (hours)* | 99 (96-113) | 104 (96-120) | 104 (96-120) | 98 (96-114) |

* Values expressed as median (range).
MAP = mean airway pressure; $FIO_2$ = fractional inspired oxygen concentration; PIP = maximum peak inspiratory pressure.

*Table 4 Primary outcome measures*

| | *Nitric oxide* | | | | *Dexamethasone* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Treatment* | *Controls* | *RR* | *95% CI* | *Treatment* | *Controls* | *RR* | *95% CI* |
| Deaths | 10 (50%) | 7 (32%) | 1.57 | 0.76-3.38 | 9 (43%) | 8 (38%) | 1.13 | 0.54-2.36 |
| CLD | 10 (50%) | 14 (64%) | 0.79 | 0.44-1.33 | 11 (52%) | 13 (62%) | 0.85 | 0.48-1.44 |
| CLD (survivors) | 10 (100%) | 14 (93%) | 1.07 | 0.71-1.37 | 11 (92%) | 13 (100%) | 0.92 | 0.67-1.28 |
| CLD/death | 20 (100%) | 21 (95%) | 1.05 | 0.84-1.25 | 20 (95%) | 21 (100%) | 0.95 | 0.79-1.18 |

RR = relative risk; CI = confidence intervals.

TREATMENT WITH INHALED NITRIC OXIDE AND DEXAMETHASONE

All infants who received both treatments or neither treatment either died or developed CLD. Six of the 10 infants (60%) receiving both inhaled NO and dexamethasone died compared with four of 11 (36%) control infants (RR 1.65, 95% CI 0.67–4.34). There were no significant differences in secondary outcome variables between the two groups.

## Discussion

This study evaluated the effectiveness of two therapeutic strategies in a selected group of preterm infants at high risk of developing CLD. The factorial design of this trial allowed the effects of two interventions to be studied, using the same sample size that would have been required to demonstrate a given effect with only one intervention. The aetiology of CLD in preterm infants is multifactorial and treatments directed towards different mechanisms of pathogenesis may be complementary. This study design not only enabled the individual effects of inhaled NO and dexamethasone to be studied, but also any obvious synergistic effect of the two treatments in combination.

At 96 hours of age, neither treatment with inhaled NO nor intravenous dexamethasone was able to prevent CLD and/or death. Additionally, there was no observed benefit when the two therapies were used in combination. Furthermore, we were unable to demonstrate any benefit in secondary outcomes such as duration of mechanical ventilation or length of hospital stay. Although the power of this study to demonstrate a small (but potentially clinically important) effect was low, the sample size was sufficiently large to have detected a magnitude of effect similar to that observed in previous trials of early dexamethasone.[3 4]

This study, to our knowledge, provides the first randomised controlled data of the use of inhaled NO in preterm infants. Several case reports and case series have been published demonstrating short term improvements in arterial oxygenation in term and preterm infants.[5 14–18] The efficacy of inhaled NO in term infants with persistent pulmonary hypertension of the newborn has also been established in three recent randomised controlled trials.[19–21] In this study, despite confirming a short term improvement in oxygenation, we were unable to show a difference in survival or respiratory outcome in our preterm infants. By applying a CLD prediction score we identified and selected a group of infants at high risk of developing CLD at 96 hours of age. In contrast to those infants in whom inhaled NO has traditionally been used, our study population included some infants who were ventilator and/or oxygen dependent without a major defect in oxygenation. Our rationale for including all high risk infants (and not restricting the use of inhaled NO to only infants with severe respiratory disease) was that inhaled NO may be beneficial in preventing the development of CLD in preterm infants through a variety of mechanisms. Although improved oxygenation is well documented, the bronchodilatory, anti-inflammatory, and anti-oedema effects of inhaled NO have received much less attention.[22–24] Conversely, there are concerns that inhaled NO treatment may have potentially damaging effects in immature lungs which could predispose an infant to CLD.[25 26] In theory, additional treatment with dexamethasone may help to protect the lung from any pro-inflammatory effects following treatment with inhaled NO. However, in this study combined treatment was no more effective than treatment with either drug alone.

Pulmonary hypertension is an almost universal early finding in infants with RDS, although clinically important extra pulmonary shunting is rare.[27 28] Treatment with inhaled NO in the acute phase of RDS and directed towards selected infants with extra pulmonary shunting may have a more pronounced effect in reducing ventilator and oxygen requirements and thereby limiting pulmonary damage.[5]

Inhaled nitric oxide may be associated with a variety of adverse effects, and haemorrhagic complications are of particular importance in the preterm infant.[29] However, although infants with an existing IVH (without parenchymal involvement) were included in this study, progression was detected only in control infants. Severe IVH may yet prove to be an important complication with earlier treatment as preterm infants are likely to be most susceptible within the first 96 hours of birth. Treatment with inhaled NO was not associated with other neonatal complications, although this study had limited power to detect a small increase in adverse events. We found no problems with methaemoglobinaemia and only one infant developed borderline high $NO_2$ concentrations during inhaled NO administration at the doses used in this study.[30 31]

In recent years several studies have investigated the effect of corticosteroid treatment in preventing CLD.[3 4 7 8] Trials of early intervention have been unable to demonstrate a consistent effect. Some infants in these studies were probably exposed to corticosteroid treatment in a situation where their risk of developing CLD was low. In this study accurate

identification of a "high risk" population using a validated prognostic score successfully ensured that exposure to treatments with potentially harmful side effects was limited to preterm infants at greatest risk. Despite having selected a high risk group, our results do not support the early use of dexamethasone. The CLD score restricted enrolment of infants into the trial until 96 hours of age. It may be that earlier intervention (perhaps within 24 hours of birth), before the development of established lung injury, is necessary to interrupt the progression towards CLD.

Our choice for the initial dose of dexamethasone was based on a previous study suggesting a beneficial effect in reducing lung injury.[4] These authors reduced the dose of dexamethasone in a subsequent study, although they had not reported an increase in adverse effects in their original study.[3] The dose of dexamethasone was reduced in the present study because of a concern about adverse gastrointestinal effects in the treated group. Two treated infants also developed fatal *Pseudomonas* septicaemia. Although a theoretical risk, previous trials of corticosteroid treatment have not reported Gram negative septicaemia occurring significantly more frequently in treated infants. In the context of this small study we are unable to draw any firm conclusions about the incidence of life threatening septic complications with corticosteroids .

In summary, this study has shown that treatment with inhaled NO confers no long term benefit in this population of high risk preterm infants. Treatment with inhaled NO was not associated with a significant increase in adverse events. Dexamethasone similarly failed to improve long term outcome. Our study targeted selected high risk infants, and as such the results are only applicable to this group and should not be interpreted as showing the treatments to have no benefit in all preterm infants. We speculate that further refinement in the identification of at risk infants, allowing earlier intervention, would be useful in directing new treatment strategies designed to prevent CLD.

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