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# Outcome predictors in nitric oxide treated preterm infants

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**Abstract** Our aim was to identify factors predictive of death in preterm infants in whom inhaled nitric oxide was administered in response to poor oxygenation (oxygenation index ≥15). Of the 23 (median gestational age 28 weeks, range 24–36) infants consecutively so treated, 15 died. Non-survival was commoner in infants with air leaks (12 of 12, $P < 0.002$) and/or a change in their oxygenation index of less than 30% in response to inhaled nitric oxide administration ($P < 0.05$).

**Conclusion** In preterm infants given inhaled nitric oxide because of poor oxygenation, a diagnosis of airleak and a lack of initial response are predictive of death.

**Key words** Air leak · Nitric oxide · Prematurity · Respiratory distress syndrome

**Abbreviations** *CLD* chronic lung disease · *ICH* intracerebral haemorrhage · *iNO* inhaled nitric oxide · *NO* nitric oxide · $NO_2$ nitrogen dioxide · *OI* oxygenation index · *RDS* respiratory distress syndrome

## Introduction

Inhaled nitric oxide (iNO) can improve oxygenation in infants with either intra- or extrapulmonary shunts [11]. iNO use has usually been reported in term infants and in that group its use has not always been associated with survival, particularly in those infants with hypoplastic or dysplastic lungs [3]. iNO has side-effects and infants born preterm may be particularly at risk. In addition, in a randomised trial [13] although use of iNO acutely improved oxygenation in prematurely born infants, it did not prevent the occurrence of chronic lung disease (CLD) or death. The infants recruited into that study [13] however were all at high risk of CLD. The aim of this study was therefore in a less selective prematurely born population, to identify criteria indicating unfavourable outcome when iNO was used as rescue therapy, as such data would be useful to guide the choice of strategy in future affected infants.

## Patients and methods

iNO was used as rescue therapy for preterm infants with clinical evidence of pulmonary hypertension with clinical and/or echocardiographic evidence of extra pulmonary shunting and in whom other therapies had failed to improve oxygenation, such that their oxygenation index (OI) was greater than or equal to 15.

$$\mathrm{OI} = \frac{\text{Mean airway pressure} \times \mathrm{FiO_2} \times 100}{\mathrm{paO_2}}$$

Use of iNO in this manner has been approved by the King's Healthcare Trust Research Ethics Committee. iNO was withheld if there was evidence of a bleeding tendency, a low platelet count (<100,000/μl) or intracerebral haemorrhage (ICH) >grade II [9]. Nitric oxide (NO) was delivered from 1000 ppm NO in a nitrogen cylinder, via a calibrated flowmeter, into the inspiratory limb of a time cycled, pressure limited, constant flow ventilator or high frequency oscillator. Monitoring of the inspired NO and its toxic oxidative product nitrogen dioxide ($NO_2$) was performed by continuous electrochemical analysis (EC90 and EC40 monitors, respectively, Bedfont, Kent, UK) which are accurate to within 5%. The NO concentration was to be reduced if the $NO_2$ level exceeded

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**Table 1** Outcome related to type and magnitude of response and pre NO OI. Data are demonstrated as *n* or median (range)

| | Died | Survived with oxygen dependency | Survived without oxygen dependency |
|---|---|---|---|
| Non-responders | 8 | 0 | 1 |
| Responders: | | | |
| sustained | 5 | 3 | 4 |
| NO dependent | 2 | 0 | 0 |
| Change in OI (%) | 26 (0–90) | 39 (−6 to 72) | 37 (31–40) |
| Pre-iNO OI | 27 (16–71) | 39 (16–46) | 20 (16–35) |

5 ppm [2]. The expiratory gases from the patient circuit passed through activated charcoal and potassium permanganate on an alumina carrier (Purafil). Three concentrations of NO were tried (10, 20 and 40 ppm) each for 20 min to identify the greatest improvement in oxygenation (optimum level) [6]. NO was continued only if there had been at least an arbitrary reduction in the OI of 30% (positive response). While the infant remained on NO, methaemoglobin levels were checked at least 24 hourly.

### Analysis

Infants were classified as non-responders (change in OI $< 30\%$) or responders, who were further sub-divided [3] according to whether the response was sustained, that is the improvement was maintained for more than 24 h, or they became NO dependent, that is iNO support was required for more than 7 days and after that time iNO withdrawal caused a deterioration. The type of response to iNO, the infant's diagnosis and the OI prior to commencing iNO were related to whether the infants died (poor outcome) or survived (good outcome). Differences were assessed for statistical significance using the chi-squared test or the Wilcoxon rank sum test.

### Patients

A total of 23 infants, median gestational age 28 weeks (range 24–36 weeks), birth weight 1200 g (range 548–3200 g) and postnatal age 2 days (range 1–14 days) were consecutively commenced on iNO at a median OI of 27 (range 16–71). The acute effect on oxygenation of iNO in certain of these patients has been reported [6]. Mothers of six infants had received antenatal steroids, 18 babies had been given surfactant postnatally. The infants who did not receive surfactant were suffering from congenital diaphragmatic hernia ($n = 1$), hydrops fetalis ($n = 2$) and congenital pneumonia ($n = 2$). Ten infants were outborn and transferred to our institution because of severe respiratory failure. Fifteen patients were transferred from conventional ventilation to high frequency oscillation because of worsening oxygenation but, despite that manoeuvre, their oxygenation remained poor and iNO was given additionally.

## Results

Of the 23 preterm infants, 15 died; four survivors were oxygen dependent beyond 28 days. Ten infants died of respiratory failure, two of sepsis, one of intractable pulmonary hypertension and two of multiorgan failure. Of the 17 infants with a primary diagnosis of respiratory distress syndrome (RDS), 13 died, one infant with a congenital diaphragmatic hernia and one of three with congenital hydrops died. Two infants with pneumonia survived. Twelve preterm infants had air leaks (five had pulmonary interstitial emphysema only, three pneumothorax only and four had both pneumothorax and pulmonary interstitial emphysema) at the time of treatment with iNO, all 12 died ($P < 0.002$). There were no significant differences between infants who died or who did not regarding their gestational age, use of antenatal steroids, surfactant or high frequency oscillation (data not shown). Two infants had ICH prior to starting iNO, the ICH did not extend and only one infant, who was unresponsive to iNO developed a grade III ICH some time after iNO had been discontinued.

Infants who did not respond to iNO were more likely to die ($P < 0.05$), (Table 1). All the infants who responded positively did so for at least 24 h. Two infants became NO-dependent; one had idiopathic hydrops fetalis and the other RDS with renal failure. Only in those two infants was discontinuation of NO associated with a deterioration in the infant's condition. No significant relationship was found between death and the pre-iNO OI (Table 1).

## Discussion

The majority of our study population showed a positive response to iNO, but 55% of the ''responders'' subsequently died. An earlier study [10] demonstrated a high mortality in immature infants given iNO, but all the mothers had had prolonged rupture of the membranes, which per se carries a significant infant mortality [1]. We do not feel the relatively high OI (≥15) we used as criteria on which to administer iNO explained our high mortality rate, as Mercier et al. [7] reported a better survival rate in preterm infants with an OI of at least 30. They [7] did not, however, include infants with airleaks and that we feel is responsible for the difference in mortality rate, as all the infants in our series who had an airleaks at the time in iNO treatment died. The high mortality rate amongst premature infants with airleaks, particularly those with poor oxygenation, has been previously highlighted [8]. We previously noted [6] that a high NO level (40 ppm) was necessary to maximise oxygenation in infants with airleak. The present data suggest it is inappropriate to expose such infants to that NO level and the attendant risk of side-effects, which include methaemaglobinaemia [4] and prolongation of the bleeding time [5] as it would not improve outcome.

Four previously reported studies [7, 10, 12, 13] have enrolled preterm infants. In one [7] an OI of 30 was used as criteria to administer and in another an OI of 19 or more [10]. In the third [12] infants were considered for iNO if they were mechanically ventilated and required

an inspired oxygen concentration of at least 50%. In the fourth [13], infants were treated with iNO if at 96 h they were deemed to be at high risk of developing CLD as defined by a modified CLD prediction score. They were all ventilated, but their baseline median inspired oxygen concentration was only 45% [13]. Our use of an OI of at least 15 is thus within the range of criteria used in those studies [7, 10, 12, 13].

Previous reports [7, 10] have highlighted the occurrence of ICH in preterm infants given iNO. In the present population ICH was uncommon, but it should be stressed that we were extremely careful to exclude infants in high risk of that complication from iNO treatment. The present results suggest our criteria were appropriate. Non survival was more common in infants with a lack of response to iNO. We used a change in OI of at least 30% to define a response to iNO. In term infants with persistent pulmonary hypertension of the newborn a poor response after 30 min of iNO was also significantly associated with non survival [7]. Unfortunately, as the mortality rate was high, the number of survivors in our series was too small to allow us to make any meaningful statement regarding iNO response and chronic oxygen dependency. Two patients became iNO dependent. This has been previously noted in ''term'' infants with developmentally abnormal lungs [3]. In the present series, however, only one of the patients had lung maldevelopment which was associated with hydrops fetalis and Mercier et al. [7] reported iNO dependence in two 26 week gestational aged infants without hypoplasia. Those [7] and our data therefore suggest that iNO dependence can also occur in patients with developmentally immature lungs.

The response to iNO used as rescue therapy in preterm infants with suspected pulmonary hypertension varies. The lack of an initial response or a diagnosis of airleak in a preterm infant with an OI $\geq$15 are associated with poor outcome. The response to iNO in infants with airleak should be assessed in a randomised controlled trial but, the 100% mortality in that population in this study, suggests a small sample size would be required.

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