Inhaled nitric oxide and intravenous magnesium sulphate for the treatment of persistent pulmonary hypertension of the newborn

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ABSTRACT

Introduction: The aim of this study was to compare the response and survival rates of term infants with persistent pulmonary hypertension of the newborn (PPHN) on high frequency oscillatory ventilation (HFOV) treated with either inhaled nitric oxide (iNO) or intravenous magnesium sulphate ($MgSO_4$).

Methods: This was a randomised controlled study. The inclusion criteria were infants with respiratory distress, oxygen index equal to or greater than 25 despite HFOV support, and echocardiographic evidence of PPHN. Infants in the $MgSO_4$ group (n is 13) were loaded with $MgSO_4$ 200 mg/kg infused over half an hour, followed by continuous infusion at 50–150 mg/kg/hour to attain a serum magnesium level of 5.0–7.0 mmol/L. Infants in the iNO group (n is 12) were administered nitric oxide at an initial concentration of 20 ppm. Analysis was done on an intention-to-treat basis.

Results: There was no significant difference in the median age when the vasodilators were commenced ($MgSO_4$ group: 14.0 hours, interquartile range [IQR]: 7.5, 27.0; iNO group: 14.8 hours, IQR: 12.5, 35.3, p is 0.8). There was no significant difference in the proportion of infants who responded primarily to either vasodilator ($MgSO_4$: 23.3%, iNO: 33.3%, p is 1.0). After switching over to iNO following a failed $MgSO_4$ therapy, a significantly higher proportion (9 out of 10) of the non-respondents in the $MgSO_4$ group recovered from PPHN and survived compared to the non-respondents in the iNO group (one out of eight) who switched over to intravenous $MgSO_4$ (p is less than 0.03).

Conclusion: Infants who were administered iNO following a failed $MgSO_4$ therapy were associated with a better outcome than those who were administered $MgSO_4$ following a failed iNO therapy.

Keywords: inhaled nitric oxide, intravenous magnesium sulphate, PPHN

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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a complex disorder that is associated with a wide array of cardiopulmonary diseases and is characterised by marked pulmonary hypertension and altered vasoreactivity, leading to the right-to-left shunting of blood across the patent ductus arteriosus and/or foramen ovale. This extrapulmonary shunting associated with high pulmonary vascular resistance causes critical hypoxaemia that is often poorly responsive to inspired oxygen or pharmacological vasodilators. Because of the associated lung parenchymal diseases, such as meconium aspiration syndrome and respiratory distress syndrome, there is often concomitant intrapulmonary shunting, further complicating the response to treatment.[1]

In recent years, inhaled nitric oxide (iNO) has been reported to be an effective selective pulmonary vasodilator for the treatment of PPHN. However, in infants with associated intrapulmonary shunt, iNO therapy alone is less effective.[2] A study that involved a randomised controlled trial reported that the combined treatment of iNO with high frequency oscillation ventilation (HFOV) produced better responses in infants with PPHN that were associated with severe lung disorders than either HFOV or iNO alone, although the response was not uniform in all infants.[3] iNo therapy is expensive, and when used at therapeutic doses, it has not been shown to improve the long-term neurodevelopmental outcome.[4] Intravenous magnesium sulphate ($MgSO_4$) has been used extensively in developing countries for the treatment of PPHN.[5-7] It is cheap and easily available, and has a potential neuroprotective effect.[8] Its main disadvantage

is that it can cause systemic hypotension. To date, no randomised controlled study comparing the efficacy of the treatment of PPHN with iNO vs. intravenous $MgSO_4$ has been reported.

The objectives of the present study were to compare the response and survival rates of term infants with PPHN on HFOV who were treated with either iNO or intravenous $MgSO_4$. Our null hypothesis was that there is no difference in the proportion of infants that respond to either treatment regimen.

METHODS

This was a randomised controlled trial carried out at the neonatal intensive care unit of the Hospital Universiti Kebangsaan Malaysia over a 37-month period, between 1 April, 2000 and 30 April, 2003. The study protocol was approved by the hospital scientific and ethics committees. Written parental informed consent was obtained before randomisation.

The inclusion criteria were infants with respiratory distress, an oxygen index (OI) ≥ 25 despite HFOV support (Sensormedic high frequency oscillator, 3100A, Yorba, Linda, CA, USA) and echocardiographic evidence of PPHN. The echocardiographic features of PPHN were a normal cardiac anatomy with right-to-left shunt at the foramen ovale and/or ductus arteriosus, with or without dilatation of the right ventricle. The exclusion criteria were infants with lethal congenital anomalies (except congenital diaphragmatic hernia), substantial bleeding diathesis (e.g. massive intracranial haemorrhage, intraventricular haemorrhage ≥ Grade 3,[9] platelet count < 50,000/L), active seizures, blood pressure that could not be stabilised, or gestational age < 34 weeks.

All infants with PPHN were on continuous cardiorespiratory, pulse oximetry, skin temperature, intra-arterial, and whenever possible, central venous pressure monitoring (SpaceLab, Redmond, WA, USA). An indwelling arterial (radial or umbilical) catheter and umbilical venous catheter (with the tip of the catheter at the level of the right atrium based on echocardiographical findings) were inserted for the monitoring of blood gases, arterial blood pressure and central venous pressure (CVP), respectively. A volume expander (normal saline 0.9% NaCl) and inotropes (dopamine and dobutamine intravenous infusions) were used to maintain the CVP and arterial blood pressure within the normal limits appropriate for the birth weight of infants. Hypoglycaemia (random blood sugar < 3.4 umol/L), metabolic acidosis, electrolyte imbalance or septicaemia, when present, were managed accordingly. Sodium bicarbonate was used for the treatment of metabolic acidosis. Infants with anaemia (Hb < 14g/dl) were given a blood transfusion. The opiate fentanyl (Duopharma, Klang, Selangor, Malaysia) was used for sedation.

The optimal mean airway pressure of HFOV used on each infant was the pressure at which the inflation of an infant's lungs was achieved, with its right hemi-diaphragm maintained at the level between the eighth-and-a-half and ninth posterior ribs radiographically. Intracranial and abdominal bleeding and/or congenital abnormalities were excluded based on ultrasonography before randomisation.

Based on their clinical features and chest radiographs, infants were stratified into one of five groups. These were: (1) respiratory distress syndrome (history of prematurity, a chest radiograph with an reticulogranular appearance, and fewer than two risk factors for sepsis); (2) pneumonia based on the presence of two or more risk factors for sepsis (such as maternal chorioamnionitis, maternal fever, positive vaginal culture for Group B *streptococcus*, a white cell count of more than 30,000 cells per mm^3 or less than 5,000 cells per mm^3, a serum C-reactive protein concentration of more than 1.0 mg/mm) and a chest radiograph with coarse opacities; (3) meconium aspiration syndrome (based on a history of meconium-stained amniotic fluid and a typical chest radiograph); (4) pulmonary hypoplasia (based on the presence of diaphragmatic hernia, a history of prolonged oligohydramnios, or hydrops foetalis); and (5) idiopathic persistent pulmonary hypertension (based on echocardiographic evidence of PPHN and a normal chest radiograph).

Each stratified group of infants was randomised in blocks of six to receive either iNO or intravenous $MgSO_4$ according to written instructions enclosed in sequentially numbered sealed envelopes that had been prepared previously by an assistant, and these were randomly shuffled five times before being numbered. Allocation concealment was not practiced and no "sham" tank of iNO was used for infants that were allocated to $MgSO_4$ therapy.

Infants assigned to the intravenous $MgSO_4$ group were given a loading dose of $MgSO_4$ at 200 mg/kg infused over half an hour, followed by a continuous infusion of a maintenance dose of $MgSO_4$ at 50–150 mg/kg/hour to achieve a serum level of magnesium of 5.0–7.0 mmol/L measured every 12 hourly. Due to the sedative effect of $MgSO_4$, once the infant was well sedated, the opiate, fetanyl was weaned off over a period of 12–24 hours.

Table I. Baseline variables of infants with PPHN treated with combined intravenous MgSO4 and HFOV vs. combined iNO therapy and HFOV.

Baseline variable	HFOV + $MgSO_4$ (n = 13)	HFOV + iNO (n = 12)	p-value
Mean birth weight ± SD (g)	3,251 ± 667	3,169 ± 351	0.7
Mean gestation ± SD (weeks)	39 ± 1	40 ± 2	0.3
Male (%)	8 (61.5)	7 (58.3)	1.0
Malay ethnic group (%)	8 (61.5)	9 (75.0)	0.5
Outborn infants (%)	9 (69.2)	8 (66.7)	1.0
LSCS (%)	9 (69.2)	6 (50.0)	0.5
Median Apgar score at 1 min (IQR)	7 (5,8)	7 (6, 8)	0.9
Median Apgar score at 5 min (IQR)	9 (7,10)	9 (6,9)	1.0

PPHN: persistent pulmonary hypertension of newborn; $MgSO_4$: magnesium sulphate; HFOV: high frequency occillatory ventilation; iNO: inhaled nitric oxide; SD: standard deviation; LSCS: lower segment caesarean section; IQR: interquartile range

Once PPHN was resolved based on echocardiographic findings, and the infants could tolerate a lower HFOV setting of a mean airway pressure (MAP) of ≤ 8 cm H_2O and a fraction of inspired oxygen (FiO_2) ≤ 0.5, the infusion of $MgSO_4$ was tailed off gradually over the next 24 hours. The weaning of the infusion of inotropes (dopamine and dobutamine) (Duopharma, Klang, Selangor, Malaysia) was carried out only after the $MgSO_4$ infusion was terminated, and when the infant's blood pressure remained stable. When hypertension developed while an infant was on $MgSO_4$, the inotropes were weaned off earlier in order to achieve a normal blood pressure, before tailing off $MgSO_4$. Re-loading of $MgSO_4$ 100–200 mg/kg infused over 30 minutes was repeated in infants who showed an initial response but reverted back to PPHN. This was then followed by the maintenance infusion of $MgSO_4$ described above. Infants who showed no reversal of PPHN after 12 hours of treatment with $MgSO_4$, or who deteriorated within four hours of the commencement of treatment (with a worsening of oxygen saturation and partial pressure of arterial oxygen [PaO_2]), were switched over to iNO therapy, and the $MgSO_4$ infusion was stopped.

Infants in the nitric oxide group were given iNO via the INOvent delivery system (Datex-Ohmeda, Madison, WI, USA). The nitric oxide was delivered from an 800-ppm cylinder to the afferent limb of the ventilator circuit of the Sensormedic high frequency oscillator via a one-way valve proximal to the humidifier. The concentrations of iNO, oxygen and nitrogen dioxide administered to the infants were monitored by the INOvent delivery system via a sampling line connected to the endotracheal tube (ET) of the infant via an ET standard-width side port connector.

Infants were given nitric oxide at a concentration of 20 ppm during the initial four hours of iNO therapy. At four hours after the onset of treatment, when an infant's condition was stable and its OI was < 20, the dosage of iNO was decreased to 15 ppm. To ensure tolerance to the weaning from iNO, the FiO_2 was increased by 0.1 for about 30 minutes before iNO was reduced. Tolerance of weaning from iNO was defined as continued patient stability and OI in two consecutive arterial blood specimens taken at 30-minute intervals following weaning, and no increment of OI by more than two from the baseline result obtained before weaning. If infants did not tolerate the weaning, they were put back on iNO of 20 ppm, and weaning would be attempted again four hours later.

For infants showing evidence of resolution of PPHN while on iNO, the iNO concentration was decreased by 5 ppm every 12 hourly till it reached 5 ppm. Subsequently, the iNO concentration was reduced by 1 ppm every four hours. Whenever an infant deteriorated within one hour of weaning (based on two consecutive OI at 30 minutes apart), the iNO concentration was adjusted to the previous level and weaning was re-attempted accordingly. To prevent a rebound of PPHN during each stage of the weaning of iNO, the FiO_2 was increased by 0.1 for a duration of about 30 minutes before being reduced to a lower level.

This was not a cross-over study. However, neonates who did not show reversal of PPHN by 12 hours of treatment with iNO at 20 ppm, or who deteriorated acutely within four hours of treatment, were switched over to $MgSO_4$ therapy. iNO therapy was then weaned off over the course of 48 hours based on their serial OI described above. The weaning of iNO was suspended if there was further deterioration of the infants' condition.

Infants were considered to have responded to the treatment of PPHN when OI < 20, the continuous pulse oximetry recorded serial rise to ≥ 90%, and repeated arterial blood gas measurements recorded a PaO_2 > 60 mmHg. PPHN was considered to have been resolved when an echocardiogram confirmed the absence of a

Table II. Comparison of the clinical variables and therapy received by the infants prior to randomisation.

Clinical variable and therapy	Randomised treatment groups		p-value
	HFOV + IV $MgSO_4$ (n = 13)	HFOV + iNO (n = 12)	
Cause of PPHN (%)			
Meconium aspiration syndrome	10 (76.9)	7 (58.3)	
Congenital diaphragmatic hernia	1 (7.7)	1 (8.3)	0.2
Others	2 (15.4)	4 (33.3)	
Chest radiograph changes (%)			
None or mild	1 (7.7)	4 (33.3)	
Moderate	9 (69.2)	5 (41.7)	0.3
Severe	3 (23.1)	3 (25.0)	
Pneumothorax (%)	1 (7.7)	2 (16.7)	0.6
Had intravenous bicarbonate (%)	5 (38.5)	4 (33.3)	1.0
On dopaminine (%)	10 (76.9)	9 (75.0)	1.0
On dobutamine (%)	7 (53.8)	9 (75.0)	0.4
On IV epinephrine (%)	5 (38.5)	4 (33.3)	1.0
On IV fentanyl (%)	12 (92.3)	7 (58.3)	0.07
Mean maximum PIP, cm H_2O (SD)	31.6 (5.0)	29.5 (8.3)	0.5
Median age when HFOV started, hours (IQR)	12.0 (3.0, 22.8)	12.8 (6.3, 26.5)	0.6
Mean OI at onset of HFOV (SD)	55.3 (28.1)	42.9 (23.4)	0.3
Mean maximum MAP when on HFOV, cm H_2O (SD)	15.8 (3.1)	12.8 (6.8)	0.3
Median OI just prior to randomisation (IQR)	39.8 (33,0, 59.0)	34.2 (17.5, 48.4)	0.2
Median age (hours) when optimal lung was achieved (IQR)	24.0 (14.0, 45.0)	24.0 (12.5, 48.8)†	0.9

HFOV: high frequency oscillatory ventilation; IV: intravenous; $MgSO_4$: magnesium sulphate; iNO: inhaled nitric oxide; PPHN: persistent pulmonary hypertension of newborn; PIP: positive inspiratory pressure; H_2O: water; OI: oxygen index; MAP: mean airway pressure; SD: standard deviation; IQR: interquartile range
* denotes statistical significance; † n = 9

right-to-left shunt. Treatment failure was defined as the persistence of the right-to-left shunt by 12 hours of life, or acute deterioration within four hours after the commencement of treatment with either of these two vasodilators. Acute deterioration was defined as a worsening of the OI and pulse oximetry readings despite treatment, after the exclusion and correction of a displaced or blocked endotracheal tube, pneumothorax, acute bleeding, septicaemia, and/or hypovolaemia.

The severity of lung disease was graded based on the criteria of Clark et al, where mild disease was indicated by minimal streaky infiltrates or reticulogranular changes with easily visualised borders of the heart and diaphragm, moderate disease was indicated by diffuse infiltrates or reticulogranular changes with obscure but visible borders of the heart and diaphragm, and severe disease was indicated by diffuse infiltrates with borders of the heart and diaphragm being difficult to visualise.[10]

The arterial blood gases and serum methaemoglobin levels of the infants were monitored using an ABL 700 series blood gas machine (Radiometer, Copenhagen, Denmark) just before administration, at one hour, and then at four-hourly intervals during $MgSO_4$ or iNO therapy. The OI of every blood gas was calculated. Echocardiograms were repeated every 12 hourly after the commencement of treatment with either vasodilator to determine whether PPHN had been resolved. Serial chest radiography was carried out at four- to six-hourly intervals during the first 24 hours, and at six- to 12-hourly intervals subsequently, until the infant was weaned off HFOV. Based on the chest radiograph findings, the MAP of HFOV was adjusted to maintain an optimal lung expansion indicated radiographically by the position of the right hemi-diaphragm at a level between the eighth-and-a-half and ninth right posterior ribs. The FiO_2 was adjusted to maintain an oxygen saturation of between 93% and 95%, and a PaO_2 of between 60 and 70 mmHg. The delta-P of HFOV was adjusted to maintain the $PaCO_2$ between 40 and 45 mmHg. In order to prevent hyperoxia and hypocarbia, all infants were placed on transcutaneous PaO_2 and partial pressure of carbon dioxide [$PaCO_2$] monitoring. The arterial blood pH was maintained at between 7.35 and 7.45. The mean arterial blood pressure was maintained at between 45 and 60 mmHg. Once an infant had achieved satisfactory blood gas results at a MAP of between 6 cm and 7 cm H_2O, with $FiO_2 \leq 0.3$, they were put on continuous positive airway pressure, or free-flow oxygen via nasal prongs.

The primary endpoint was the resolution of PPHN based on the echocardiography findings and an OI < 15.

Table III. Comparison of clinical outcomes of infants with PPHN treated with combined IV MgSO4 and HFOV vs. combined iNO therapy and HFOV.

Outcome variable	HFOV + IV $MgSO_4$ (n = 13)	HFOV + iNO (n = 12)	p-value
Deteriorated acutely within 4 hours of treatment with assigned vasodilator (%)	4 (30.8)	3 (25.0)	1.0
PPHN resolved(%):			
With assigned vasodilator	3 (23.1)	4 (33.3)	0.03*
After crossing over	9 (69.2)	1 (8.3)	
PPHN unresolved(%):			
Died before crossing over	0	4	
After crossing over	1 (7.7)	3 (58.3)	
Highest met haemoglobin level in % of total Hb, median (IQR)	1.2 (0.9, 1.3)	1.5 (1.3, 1.8)	0.7
Lowest mean blood pressure during treatment, mmHg, median (IQR)	32 (26.5, 38.5)	33.5 (21.0, 39.3)	0.8
Median duration of ventilation, days (IQR)	5.5 (3.3, 10.8)	4.0 (1.5, 10.0)	0.3
Median duration of hospitalisation, days (IQR)	13.5 (4.6, 28.8)	5.0 (2.3, 12.0)	0.1
Alive at discharge (%)	8 (61.5)	2 (16.7)	0.004*

Outcome variable	HFOV + IV $MgSO_4$ (n = 5)	HFOV + iNO (n = 10)	p-value
Median age at death, days (IQR)	4.5 (3.0, 7.5)	5.0 (1.9, 7.5)	1.0
Cause of death (%)			
PPHN	0 (0)	3 (30)	
Non-PPHN			
Asphyxia with multi-organ failure	0	2	-
Sepsis	2	4	
Pneumothorax	2 (100)	0 (70)	
Others	1	1	

HFOV: high frequency oscillatory ventilation; IV $MgSO_4$: intravenous magnesium sulphate; iNO: inhaled nitric oxide; PPHN: persistent pulmonary hypertension of newborn; IQR: interquartile range
* denotes statistical significance;

The secondary endpoint was survival at discharge. The assessment of the outcome was not blinded. Based on the results of other studies,[2,3,5,6] the response rate of one group was estimated to be 95%, while that of the second group was 80%. In order to be able to detect a difference of 15% response rates between the two groups of infants with a 95% level of confidence and a power of 85% (two-tailed test), a calculated sample size of 152 infants (76 infants per group) needed to be recruited during the study period.

Statistical analysis was done on an intention-to-treat basis. The variables of the infants receiving the two treatment regimens were compared. The categorical variables were evaluated using a two-tailed chi-square test (or Fisher's exact test when there were cells with an expected value of < 5). The continuous variables were compared using a two-tailed *t*-test (for normally distributed data) or Mann-Whitney U-test for data with a skewed distribution. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

During the study period, 36 infants were admitted with PPHN. 11 infants were not recruited into the study for the following reasons: PPHN was reverted by HFOV prior to randomisation (n = 2), no parental consent was obtained (n = 1), a persistently low platelet count (n = 1), not able to stabilise the blood pressure (n = 6), and died before randomisation (n = 1). There was no significant difference in the ethnic distribution (p = 0.08), gender distribution (p = 0.8), proportion of outborn infants (p = 0.7), mean birth weight (p = 0.2), median gestational age (p = 0.9), lower segment Caesarean rates (p = 0.5), mean Apgar score at one minute of life (p = 0.3) and median Apgar score at five minutes of life (p = 0.3) between infants recruited and not recruited into the study.

After recruiting 25 infants (16% of the calculated sample size), an interim analysis was carried out. Because of the unacceptably high mortality rate (> 80%) in one of the treatment groups, the study was terminated prematurely before the calculated sample size was achieved. The following are the results of the infants recruited into the study. Among the 25 infants recruited, 13 were randomised into the $MgSO_4$ group and 12 into the iNO group. There was no significant difference in the mean birth weight, mean gestational age, gender distribution, place of delivery, lower segment Caesarean section rates, and median Apgar scores between these two groups of infants (Table I).

There was also no significant difference in the causes of PPHN, the severity of chest radiograph changes, pneumothorax, treatment with sodium bicarbonate and inotropes (dopamine, dobutamine and epinephrine), and treatment with opiates between these two groups of infants (Table II). Neither was there any significant difference in the maximum ventilatory pressure received, the age of onset of HFOV, the mean OI at the commencement of HFOV, and the median age at which optimal lung volume was achieved between the two groups. Although the median OI of infants in the $MgSO_4$ group just prior to randomisation was higher than that of the iNO group, the difference was not statistically significant ($p = 0.2$).

There was no significant difference in the median age when the vasodilators were started after randomisation ($MgSO_4$ group: 14.0 hours, interquartile range [IQR]: 7.5, 27.0; iNO group: 14.8 hours, IQR: 12.5, 35.3) ($p = 0.8$) between the two groups. There was no significant difference in the proportion of infants who deteriorated acutely within four hours of commencement of either vasodilator (Table III). Neither was there any significant difference in the proportion of infants responding to the primary vasodilator that was assigned. A significantly higher proportion of non-respondent infants in the $MgSO_4$ group recovered from PPHN and survived after switching over to iNO than the non-responders in the iNO group who switched over to intravenous $MgSO_4$. There was no significant difference in the highest recorded met haemoglobin levels, the mean blood pressure during treatment, the duration of ventilation and the duration of hospitalisation between the two groups of infants. No infant developed a bleeding tendency of chronic lung disease. Overall, infants randomised to the $MgSO_4$ group had a significantly higher survival rate than those in the iNO group (Fig. 1). Unlike infants in the iNO group, none of the infants in the $MgSO_4$ group died because of PPHN (Table III). There was no significant difference in the age of death between the two groups. No autopsy was conducted on any of the infants who died.

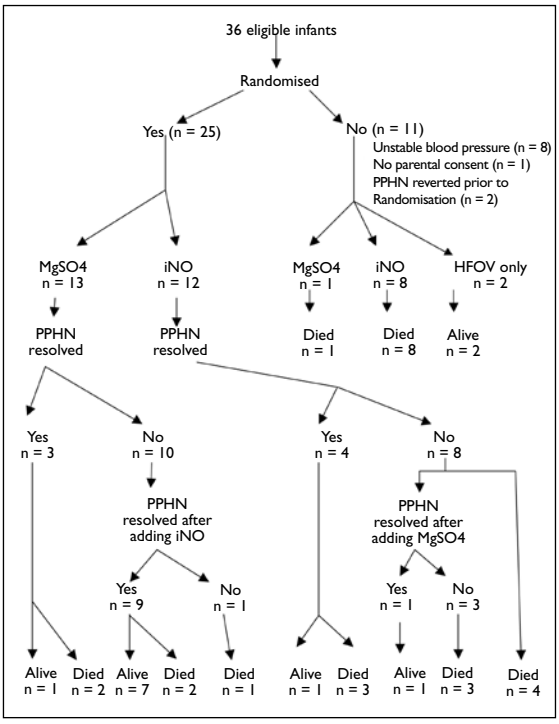

Fig. 1 The treatment received and outcomes of 36 eligible infants during the study period.
MgSO4: magnesium sulphate; iNO: inhaled nitric oxide; HFOV: high frequency oscillatory ventilation

DISCUSSION

The baseline data, clinical variables and therapies received by the infants prior to randomisation were comparable in both groups. Although not statistically significant, a higher proportion of infants in the $MgSO_4$ group received intravenous fentanyl. As fentanyl has some pulmonary vasodilator effects, it is not certain to what extent it might have influenced the outcomes of our patients in the present study.

Many patients in the present study were very ill infants with severe PPHN, as reflected by their high median OI of 53.2, which met the eligibility criteria for extracorporeal membrane oxygenation (ECMO). In many developing countries, such as Malaysia, facilities for ECMO are not available for infants with severe PPHN who are not responding to ventilatory support. Individually, both intravenous $MgSO_4$ and iNO have been reported to play beneficial roles in reverting PPHN in some infants.[2-7] Based on the results of the present study, it is speculated that in infants with very severe PPHN, providing iNO therapy following failed $MgSO_4$ therapy may be associated with a better outcome than providing $MgSO_4$ therapy following failed iNO therapy.

Magnesium modulates vasoactivity by affecting the influx of extracellular calcium ions Ca^{2+}.[11-13] Various investigators have observed that the oxygenation in infants with PPHN who responded to $MgSO_4$ began to increase after about one hour of $MgSO_4$ infusion and increased significantly at six hours after the initiation of therapy.[5,7] As $MgSO_4$ therapy can cause systemic hypotension, the concurrent use of inotrope to maintain these infants' blood pressure is mandatory. In contrast, iNO at doses of less than 100 ppm is a selective pulmonary vasodilator, by promoting the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) mediated by soluble guanylate cyclase in the vascular smooth muscle.[14] Its vasodilator

effect in patients responding to treatment could be observed within 15 minutes after the commencement of therapy, and its maximum effect could be attained within the first hour of therapy.[15] Thus, compared with iNO therapy, intravenous $MgSO_4$ infusion has a much slower onset of action on PPHN and takes a longer time to exert its maximum benefit.

A high proportion of infants failed to respond to the vasodilators that they were randomised to receive in the present study. One possible explanation for this could be that many of them had severe parenchymal lung diseases with a significant intrapulmonary shunt. Other investigators have previously reported that the vasodilator effect of iNO was more pronounced for PPHN associated with an extrapulmonary shunt than PPHN associated with an intrapulmonary shunt developed commonly in patients with severe parenchymal lung disease.[2,16] We did not consider increasing the dosages of $MgSO_4$ or iNO during the study as they have been previously reported to be the optimal maximal dosages with minimal side effects.[2,3,5,6,16]

$MgSO_4$ and iNO produce pulmonary vasodilatation through different mechanisms.[11-14] The results of this study showed that infants with previous exposure to $MgSO_4$ therapy responded to the subsequent administration of iNO. In contrast, infants who failed to respond to iNO used as the primary vasodilator were less likely to respond to subsequent $MgSO_4$ therapy. The better outcome of infants treated with iNO therapy after previous exposure to intravenous $MgSO_4$ could be due to the combined effect of the sustained vasodilator action of $MgSO_4$ and the rapid onset of action of iNO. In contrast, the poorer outcome among infants who did not respond to initial iNO therapy and were subsequently provided with intravenous $MgSO_4$ therapy could be due to the relatively slow onset of action of $MgSO_4$. In the presence of severe PPHN, this group of infants deteriorated rapidly and died before $MgSO_4$ could take effect. However, as this was not a cross-over study, it is too premature for us to speculate that $MgSO_4$ has a priming effect for the successful treatment of iNO therapy, as was reported previously in an animal study.[17] Further appropriately designed randomised controlled trials of adequate sample size should be carried out to address this issue.

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