Original Article

Neurodevelopmental Outcome of Newborns with Persistent Pulmonary Hypertension

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Abstract

Background: **Developmental disabilities have been reported in infants with persistent pulmonary hypertension of the newborn (PPHN) treated with inhaled nitric oxide (INO) or intravenous magnesium sulphate ($MgSO_4$) and/or extracorporeal membrane oxygenation. This paper reports the rate of developmental disabilities at 2 years of age in a cohort of survivors of PPHN treated with INO, $MgSO_4$, or both during the neonatal period.**

Methods: **Sixteen survivors of PPHN were prospectively followed up. These infants were treated with intravenous $MgSO_4$ and/or INO during the neonatal period. Neurodevelopmental assessment was carried out at 2 years of age using the Bayley Scales of Infant Development 2nd Edition by a developmental psychologist. Eleven (68.8%) infants completed the 2-year follow-up.**

Results: **The median mental developmental index (MDI) and physical developmental index scores were 85 (interquartile range, IQR = 27) and 87 (IQR = 33), respectively. Two infants (18.2%) had developmental disability (MDI scores <70).**

Conclusion: **Survivors of PPHN are at risk of developmental disabilities. Early intervention programme and long-term follow-up should be integrated in the management of these infants.**

Keywords: *developmental disabilities, magnesium sulphate, neurology, nitric oxide, persistent pulmonary hypertension of newborn*

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome that is associated with a variety of neonatal cardiopulmonary diseases, including meconium aspiration syndrome (MAS), hyaline membrane disease, pneumonia, and congenital diaphragmatic hernia. Significant hypoxaemia with right-to-left shunting across a patent foramen ovale, ductus arteriosus, or both, are clinical hallmarks of PPHN. The mortality rate was high (11%–48%), and PPHN is the most common indication for infants needing extracorporeal membrane oxygenation, ECMO (1).

Recently, new therapeutic modalities, such as inhaled nitric oxide (INO), have been used in the treatment of PPHN (2). INO acts as a pulmonary vasodilator by activating guanylate cyclase, which leads to an increase in the production of cyclic guanosine monophosphate that causes vascular smooth muscle relaxation. However, INO therapy is expensive and only widely available in developed countries. Intravenous magnesium sulphate ($MgSO_4$) has been used as a vasodilator in the treatment of PPHN in some developing and developed countries (3–5). The disadvantage of $MgSO_4$ treatment is that it causes systemic vasodilation, and hypotension is a common side effect.

Infants with PPHN become critically ill during the neonatal period and are at risk for adverse neurodevelopmental outcomes. Severe neurodevelopmental disability was reported to occur in 11.8% by 1 year of age and 12.1% by 2 years of age in a group of infants who was treated for PPHN with INO during the neonatal period (6). Lipkin et al. (7) reported the outcome at 1 year of age in 133 infants with moderately severe PPHN who were treated with INO. Major neurologic abnormalities, cognitive delays, and hearing loss were present in 13%, 30%, and 19% of infants, respectively. Tolsa et al. (4) showed that 11 infants with PPHN who were treated with intravenous $MgSO_4$ had normal neurodevelopment at 6 and 12 months of age. However, in another study

(5), major neurodevelopment impairments in preschool-age children were reported to occur in 11.5% of children who were treated with $MgSO_4$ for PPHN.

This study examined the neurodevelopmental outcome at 2 years of age for a group of PPHN survivors who were treated with intravenous $MgSO_4$, INO, or both during the neonatal period.

Subjects and Methods

Thirty-eight term and near-term infants (more than 34 gestational weeks) with PPHN were admitted to the Neonatal Intensive Care Unit, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, over a 3-year period between April 2000 and April 2003. The unit is a level III neonatal intensive care unit that offers a wide range of services, except ECMO. Twenty-five (65.8%) of the infants were involved in a randomised controlled trial (RCT) comparing the effectiveness of intravenous $MgSO_4$ and INO in term infants with PPHN (8).

The PPHN diagnosis was based on the echocardiographical evidence of right-to-left shunting of blood across the ductus arteriosus and/or the foramen ovale in newborns with severe hypoxaemia (oxygenation index, OI, of more than 25). All infants were on a high frequency oscillatory ventilator (Model 3100A; Sensor Medics, Yorba Linda, CA) support.

The infants in the RCT were managed according to the following protocol. Infants in the intravenous $MgSO_4$ group were administered a loading dose of $MgSO_4$ at 200 mg/kg infused over half an hour, followed by a continuous infusion of $MgSO_4$ at 50–150 mg/kg/hour to achieve a serum magnesium level of 5.0–7.0 mmol/L. Infants in the INO group were administered an initial dose of 20 ppm via the INOvent delivery system (Datex-Ohmeda, Madison, WI, USA). The vasodilator treatment was switched to the other vasodilator when the infant developed acute deterioration in the pulse oximetry or in the OI during the first 4 hours of treatment, or if the right-to-left shunt persisted beyond 12 hours of life. The first vasodilator was removed over 12–24 hours. The vasodilator that the infant responded to was removed once the PPHN resolved based on the echocardiographical findings, and the infants tolerated a lower high-frequency oscillatory ventilation setting with a mean airway pressure of 8 cm H_2O or less and a fraction of inspired O_2 of 0.5 or less. The infusion of $MgSO_4$ was gradually decreased over the next 24 hours. The INO was reduced by 5 ppm every 12 hours until it reached 5 ppm, and then it was reduced by 1 ppm every 4 hours. Serial chest radiographs were used to ensure optimal lung inflation to the $8^{1/2}$ or 9th rib. The level of pCO_2 was kept between 35 and 50 mmHg. Infusions of dopamine and/or dobutamine were used to maintain normal blood pressure (mean arterial pressure at the 50th percentile for gestational age). Metabolic acidosis was treated with sodium bicarbonate.

Infants whose parents did not provide consent for the RCT were managed in the same manner as the infants involved in the RCT except for the choice of vasodilator therapy. They were started on INO, and $MgSO_4$ infusion was used as the first vasodilator when contraindications to INO (e.g., coagulopathy and bleeding diathesis) were present. The infants who did not respond to INO were switched to the $MgSO_4$ infusion. The same weaning strategy was used for these infants.

Follow-ups for the survivors occurred at our clinic at 3, 6, 12, 18, and 24 months of age. During these visits, parents were interviewed regarding their children's feeding, intercurrent illnesses, re-hospitalisations, and developmental milestones. The growth parameters were measured and physical and neurological examinations (Amiel-Tison et al., 9) were performed by the neonatologists. Hearing tests using brainstem auditory evoked potentials were performed within 6 months of being discharged from the hospital. The hearing test was repeated at 1 year of age if the first test was normal, but earlier if it showed any abnormality. At 24 months of age, the children were assessed using the Bayley Scales (2nd edition), by a clinical psychologist who was not involved in the care of these children during the neonatal period. For an infant who was born at or before 36 weeks of gestation, the assessment was performed at 24 months for the corrected age.

Abnormal growth was defined as body weight and length below the 10th percentile on the National Centre for Health Statistics growth chart. An adverse neurodevelopmental outcome was defined as a score of less than 70 on either portion of the Bayley Scales, an abnormal finding on the neurological examination, or both.

The data were analysed using the SPSS version 12.0.1 (SPSS Inc., Chicago, IL). The Mann–Whitney U test was used to compare the findings between infants receiving different vasodilator therapies. A P value of less than 0.05 was considered significant.

Results

Overall, 16 (42.1%) of the 38 infants survived until discharge. However, only 11 (68.75%) survivors completed the 2-year follow–up; 7 of these infants were involved in the RCT. The other 5 survivors defaulted on the follow-up and could not be located. The demographic characteristics and clinical data of the infants are shown in Table 1. The majority of the infants were males (n = 8, 72.7%). Their mean gestation and median birth weight were 39 weeks (SD 1.89) and 3050 g (IQR 2720, 3670), respectively, and 9 (81.8%) had MAS.

Seven (63.6%) of the infants received both INO and $MgSO_4$, and 4 infants received INO alone (Table 2). The median mental developmental index (MDI) and psychomotor developmental index (PDI) scores of the survivors were 85 (IQR 27) and 87 (IQR 33), respectively. Two infants scored less than 70 on the Bayley's testing for MDI (Table 2). One of them (infant no. 4) had moderate PPHN (maximum OI of 39) and was ventilated for 21 days. The other (infant no. 9) had grade 2 hypoxic ischaemic encephalopathy according to modified Sarnat staging (10); this infant also had severe PPHN (maximum OI of 160), and the OI decreased to less than 25 only after 67 hours. Both infants received INO and $MgSO_4$ therapy.

Even though the number of infants who completed the follow-up was small, we attempted to compare the outcome in infants who received INO alone with those who received the combined INO and $MgSO_4$ therapy. In comparison with the infants who received INO alone, those who received the combined therapy had higher OI levels, with a median (IQR) of 53.2 (20.6), and a longer duration of OI of more than 25, with a median (IQR) of 44 hours (51.2), compared with those who received the INO alone, with a median (IQR) of 38.9 (27.5) for OI level (P = 0.4) and 14.5 hours (13.0) for duration of OI of more than 25 (P = 0.4). The infants who received the combined therapy had higher MDI scores, with a median (IQR) of 92 (45), and higher PDI scores, with a median (IQR) of 92 (48), compared with those receiving INO alone, with a median (IQR) of 84.5 (17.5) for MDI score and 85.5 (12) for PDI score; however, these differences were not statistically significant (P = 0.9 for MDI and P = 0.5 for PDI).

None of the 11 survivors had feeding difficulties, eye/hearing problems, or an abnormal neurological examination. One infant had failure to thrive, whereas 4 (36.4%) had hyper-reactive airway problems.

Table 1: Demographic and clinical data from survivors of persistent pulmonary hypertension of the newborn

Case no.	Sex	Gestation (weeks)	Birth weight (g)	5-minute Apgar score	Respiratory diagnosis
1	F	39	37003	10	MAS
2	M	41	3300	9	MAS
3	F	39	2850	5	MAS
4	M	42	3670	9	MAS
5	M	38	3050	8	MAS
6	F	38	2800	10	Pneumonia
7	M	39	3360	8	MAS
8	M	35	2080	9	RDS
9	M	39	3740	6	MAS
10	M	38	2720	9	MAS
11	M	41	2605	9	MAS

Abbreviations: M = male, F = female, MAS = meconium aspiration syndrome, RDS = respiratory distress syndrome

Table 2: Vasodilator therapy, clinical parameters, and mental and physical developmental index scores of the survivors of persistent pulmonary hypertension of the newborn

Case no.	Vasodilator	Highest OI	Duration of OI > 25 (hours)	Duration of ventilation (days)	MDI score	PDI score
1	INO + $MgSO_4$	89.8	78.0	8.0	114	92
2	INO	28.0	13.0	4.0	81	73
3	INO + $MgSO_4$	32.0	n/a	11.0	92	125
4 *	INO + $MgSO_4$	39.0	32.0	21.5	58	77
5	INO	37.7	14.5.0	16.0	84	88
6	INO + $MgSO_4$	n/a	22.0	10.0	103	121
7	INO + $MgSO_4$	59.0	56.0	21.0	100	106
8	INO	63.8	n/a	12.0	85	87
9 *	INO + $MgSO_4$	160.0	67.0	10.0	50	54
10	INO + $MgSO_4$	47.4	8.5	6.0	76	73
11	INO	40.0	47.0	5.0	104	84

* Infants with MDI score of less than 70.
Abbreviation: INO = inhaled nitric oxide, $MgSO_4$ = magnesium sulphate, OI = oxygenation index, MDI = mental developmental index, PDI = psychomotor developmental index, n/a = not available

Discussion

The rate of an adverse neurodevelopmental outcome at 2 years of age in our survivors was 18.2%. However, comparing our findings with previously reported neurodevelopmental outcomes is difficult because of the differences in the criteria for the treatment and management strategies and outcome measures (3–6,11–13) Many studies examined infants who were treated with either $MgSO_4$ or INO. The majority (63.6%) of our patients received both vasodilators. The infants in our study were very ill, which was demonstrated by a high median OI of 53.2. The majority of these infants met the eligibility criteria for an ECMO referral (OI of 40 or more). Ichiba et al. (11) reported a 6.7% adverse outcome rate at 3 years of age among the 15 survivors with moderately severe PPHN (mean OI 27.2, SD 15.2). Furthermore, they reported that a normal neurodevelopmental outcome was significantly higher in the infants who responded early to the treatment (OI of less than 10 within 1 hour). The majority of our patients had a high OI for prolonged periods. Because of the small sample size, it was not possible to determine whether a combination of INO and $MgSO_4$ therapy was associated with a better neurodevelopmental outcome, although the trend suggested that the combination therapy was associated with a higher MDI and PDI in infants with a more severe PPHN.

These infants should undergo a longer term follow-up evaluation because they are still at risk of neurodevelopmental impairment and behavioural problems. Galli et al. (4) found a major impairment in 6% at 18 months and 11.4% at 5 years old in a group of 33 infants with PPHN who were treated with $MgSO_4$. Behavioural problems were reported to be higher among 2- to 4-year-old PPHN survivors than the rate of 14% among reference populations (12). Berti et al. (13) reported that 26% and 22% of the PPHN survivors who were assessed at a mean age of 41 months had behavioural problems and language disturbances, respectively.

Conclusion

Our study indicated that the survivors of PPHN have a high risk of adverse neurodevelopmental outcomes. Early intervention program and long term follow-up should be integrated in the management of these infants.

Authors' Contributions

Conception and design, obtaining of funding, critical revision of the article: NYB
Provision of patients: VC, RS
Collection and assembly of the data: NYB, VC, RS, JR
Analysis and interpretation of the data: JR, NYB
Drafting of the article: JR

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