MAGNESIUM SULPHATE IMPROVES THE OUTCOME IN PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Sarar Mohamed, Tom Matthews, David Corcoran, Tom Clarke.

Rotunda Hospital, Dublin, Republic of Ireland

Abstract

Background: Persistent pulmonary hypertension of the newborn (PPHN) is a potentially life threatening disorder with a mortality of 10-20%. Current treatment strategies include mechanical

Ventilation, surfactant replacement, vasodilator agents, inhaled nitric oxide and ECMO.

Aims: The aim of this study was to determine the efficacy of MgSo4 in the treatment of PPHN.

Methods: This study is a retrospective review of infants with PPHN who were treated with magnesium Sulphate in a tertiary neonatal centre over five years, 1995-2000. The primary outcome measures were

reduction in Oxygenation Index (OI) and survival with normal neurodevelopmental examination.

Results: Thirty-one newborn infants who received MgSo4 therapy for PPHN were reviewed. Twenty- five infants were > 34 weeks gestation. Fifteen infants had birth asphyxia, 8 (25%) had meconium aspiration syndrome, three had primary PPHN and two had congenital diaphragmatic hernia. The OI decreased significantly after 12 hours of magnesium sulphate infusion from 27 to 17 mm Hg ($P < 0.001$). The primary outcome showed that

27 patients (87%) survived with normal neurodevelopmental examination. Three patients were treated with nitric oxide therapy; one of them failed nitric oxide and responded to ECMO. One patient has cerebral palsy and two have hypertonia and dyskinesia.

Conclusion: MgSo4 appears to be safe and effective in this cohort. It may have a place in the treatment of PPHN especially in areas where NO and ECMO is not available.

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; OI, oxygenation index; ECMO, extra corporal membrane oxygenation; CDH, congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; MgSo4, magnesium sulphate.

Introduction:

Persistent pulmonary hypertension of the newborn (PPHN) is a potentially life-threatening disorder that complicates the transition from fetal to postnatal life. It is characterised by profound hypoxemia, high pulmonary vascular resistance and right to left shunting across the ductus arteriosus or the foramen ovale.[1,2,3] The prevalence of PPHN in the UK is 1:1400 to 1:1700. The prevalence in North America is two to five times higher than that seen in the UK.[4,5]

The available treatment strategies for PPHN include optimum conventional or high frequency oscillatory ventilation, systemic vasodilators, inhaled nitric oxide and ECMO.A numbers of agents that dilate the pulmonary vasculture were investigated for a possible role in the treatment of PPHN. Prostaglandin, prostacyclin, and tolazoline have been tried with variable success. The main side effect of these drugs was systemic hypotension. Randomised controlled trials of inhaled nitric oxide have shown benefits in oxygenations and avoiding ECMO in

neonates with PPHN. [3,6-11.]

Magnesium sulphate was introduced for the treatment of PPHN in 1992. A few studies evaluated the role of magnesium sulphate in treatment of PPHN were published in the last decade.12,13,14. These studies enrolled only 7 to 11 infants.

The aim of this study was to determine the efficacy of magnesium sulphate in the treatment of PPHN.

Methods and subjects

This is a retrospective review of infants with PPHN treated with magnesium sulphate in a tertiary neonatal centre in Dublin, from 1995 to 2000.

All charts were reviewed. Information taken from the charts include gestational age,

Apgar score, birth weight, primary diagnosis, ventilator settings, arterial blood gas results and neurodevelopmental assessment. Magnesium sulphate was used as a loading dose of 200 mg/kg followed by an infusion of 20-100 mg/kg/hour to keep the magnesium level between 3.5 and 5.5 mg/dl. All infants

showed persistent hypoxemia despite adequate ventilation before treatment with magnesium sulphate was commenced. Infants were sedated with morphine.

The primary outcome measure was reduction in the oxygenation index and survival with normal neurodevelopmental examination. The oxygenation index was calculated using the following formula: Fio2 x MAP X 100/Po2. (Where Fio2 is fractional inspiratory oxygen, MAP is mean airway pressure, and Po2 is arterial oxygen tension).

Patients were followed up in the paediatric outpatient clinic for

15 to 24 months where the neurodevelopmental outcome was assessed.

Paired t test was used to compare values at various intervals during treatment with magnesium sulphate. P value <0.05 was considered as significant.15

Results

A cohort of 31 infants was treated with magnesium sulphate during the study period. Twenty five-infants were term or near term (>34 weeks). Three patients were less than 30 weeks gestation. Half of our patients had birth asphyxia as shown in table

The diagnosis of birth asphyxia was based on: abnormal CTG, cord ph <7.1, and Apgar score <3 at 1 minute. Eight patients had meconium aspiration syndrome while three had primary PPHN. Two patients who had congenital diaphragmatic hernia were treated with MgSo4 preoperatively.

The mean (SD) baseline OI before starting MgSo4 was 27 (15.7) mm Hg as shown in table 3. It was significantly lower after 12 hours of treatment, 17 (13.9) mm Hg. P value was <0.001. The FiO2 (mean, SD) was significantly decreased from 0.91 (0.14) before commencing MgSo4 to 0.78 (0.12) after 12 hours of treatment (P < 0.001).

The mean (SD) arterial partial pressure of oxygen showed significant increase from 6.45 (2.1) Kpa at the baseline to 8.9 (2.4) Kpa after 12 hours of magnesium infusion (P <0.001). Twenty-seven infants (87%) responded clinically to magnesium therapy, which was shown by improved oxygenation. Three patients did not show adequate clinical improvement with magnesium therapy and subsequently treated with inhaled nitric oxide. One of these patients failed nitric oxide therapy and

responded to ECMO. The mean (SD) duration of magnesium treatment was 40 (14) hours. Magnesium therapy was not associated with significant hypotension or bradycardia.

The primary outcome showed that 27 infants (87%) survived to discharge home with normal neurodevelopmental examination. One patient died on the second day of treatment with magnesium sulphate. Twenty-five patients were available for follow up at the age of 15 to 24 months. Twenty-two infants have normal neurodevelopmental examination. One infant has cerebral palsy, while two patients have hypertonia and dyskinesia.

Table 1. Patients Characteristics

Characteristic	**No (%)**
Sex	
Male	20 (65)
Female	11 (35)
Gestational age	
<30 weeks	3 (10)
30-34 weeks	3(10)
>34 weeks	25(80)
Apgar @ 1 minute	
0-3	15(47)
4-6	10(33)
4-7	6(20)

Table 2. Primary Diagnosis

Diagnosis	No. (%)
Birth asphyxia	15(47)
MAS	8 (25)
Primary PPHN	3 (11)
CDH	2 (6)
Others	3(11)

Table 3. Clinical parameters (mean SD) in relation to treatment (in hours)

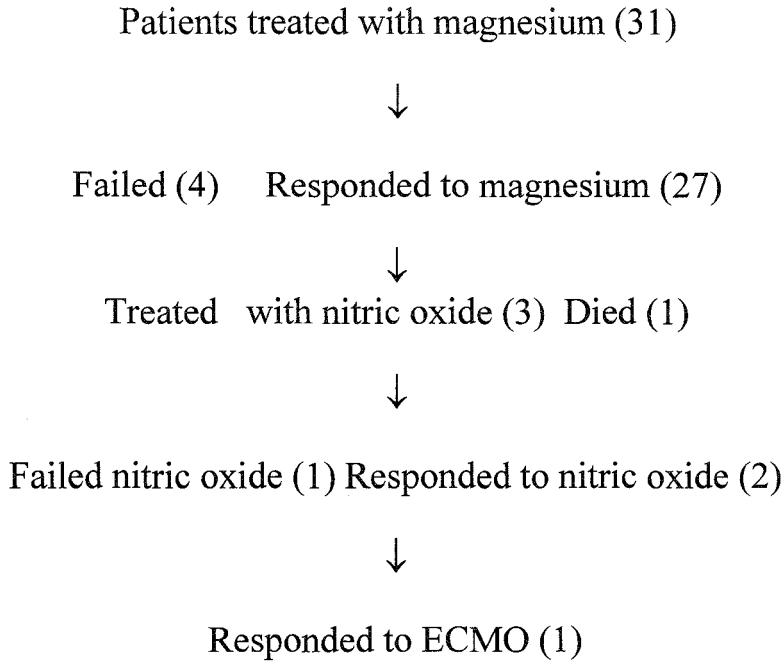
Parameter	Baseline	12	24	48	72	P
Heart rate	133(17)	132(15)	125(18)	123(15)	143(12)	0.87
Systolic BP	50(7)	48(8)	50(6)	54(6)	54(5)	0.85
PO2	6.4(2.1)	8.9(2.4)	8.9(2.2)	9.9(2.1)	10.2(2)	0.001
FiO2	91(14)	78(12)	68(11)	57(14)	39(11)	0.001
OI	17(15)	17(13)	15(9)	8(3)	7(2)	0.001

BP in mm Hg, PO2 in Kpa, and OI in mm Hg

Table 4.Long term neurodevelopmental outcome

Outcome	No (%)
Normal	21 (87)
Cerebral palsy	1 (3.3)
Dyskinesia	1 (3.3)
Hypertonia	1 (3.3)

Figure 1. Patients Flow Diagram



Discussion

There is a limited experience with the use of magnesium sulphate

in the treatment of PPHN. Magnesium therapy was introduced in our institute in 1995 after preliminary report published by Abu Osba et al.12 Most of our patients were term or near term, which is expected, as PPHN is more common in this gestational age group.

Three preterm infants, less than thirty weeks gestation, were treated with magnesium sulphate and responded well. This agrees with Wu et al who reported good clinical response to magnesium therapy in a small cohort of premature infants.[14]

The baseline oxygenation index in this series was relatively high; mean (SD) 27(15.7) mm Hg. This reflects the degree of severity of PPHN. According to the published criteria, OI of [15] mm Hg is an indication to start nitric oxide therapy while ECMO is indicated when the OI is 25 mm Hg. Oxygenation index of 40 mm Hg is predictive of 80% mortality[9, 11,12]

The OI and FiO2 were reduced significantly after 12 hours of starting magnesium infusion. This improvement in oxygenation indicates a drop in the pulmonary arterial pressure and vascular resistance and increase in oxygen delivery to the tissues. These short-term benefits were not associated with significant drop in the systemic blood pressure as seen with other vasodilators like tolazoline.[6,7,8] Abu-Osba, Tolsa and Wu reported similar clinical improvements.[12, 13,14]

The survival rate with normal neurodevelopmental outcome was high in this series compared with the previous studies. Clinical benefits observed in clinical trials of nitric oxide have not been

translated into improvement in survival rate.[3]

The long-term neurodevelopmental outcome in this cohort was acceptable compared with the published data. 16Lipkin et al studied the neurodevelopmental outcome in 133 infants with PPHN treated with nitric oxide.18They found major neurological abnormalities in 13%, cognitive delay in 30%, and hearing loss in 19% of the infants.

Two of the three patients who failed magnesium therapy in this study, had congenital diaphragmatic hernia. The third infant had lung hypoplasia. Congenital diaphragmatic hernia has remained the most difficult condition to treat successfully despite all the advances in neonatal critical care. This probably reflects our limited understanding of the pathophysiology of this anomaly.[17,18,19,23]

In this series magnesium sulphate therapy appears to be a safe and effective treatment for PPHN. We believe that nitric oxide is the standard treatment for PPHN, however it is not available in many small neonatal units. Magnesium sulphate may have a place in the management of PPHN in areas where nitric oxide and ECMO is not available. A prospective randomised controlled trial may be justified to evaluate the place of magnesium therapy in PPHN.

References

1.Roberts J, Philip W. Advances in the treatment of persistent pulmonary hypertension of the newborn. Clin Perinatol 1998; 25: 984-1004.

2. William A. Persistent pulmonary hypertension of the neonate. In Polin A, Yoder M, Burg F (eds): Workshop in practical neonatology, 3rd ed. W. B. Saunders, 2001, pp 229-312.

3. Greenough A, Roberton N. Acute respiratory disease in the newborn. In Rennie J, Roberton N (eds): Textbook of neonatology, 3rd ed. Churchill Livingstone, 2000, pp 418-607.

4. Hjalmarson O. Epidemiology and classification of acute neonatal respiratory disorders. Acta Paed Scan1981; 70: 773-783.

5. Reece E, Moya F, Yakigi R et al. Persistent pulmonary hypertension: assessment of perinatal factors. Obst Gyn 1987; 70: 696-700.

6. Cutis J, Palacino J, O'Neill J. Endotracheal administration of tolazoline in hypoxia induced pulmonary hypertension. Pediatrics 1993; 92:403-408.

7. Bindl L, Fahnenstich H, Peukert U. Aerosolized prostacyclin for pulmonary hypertension in neonates. Arch Dis Child 1994; F214-F216.

8. Zobel G, Dacar D, Rodl S, Friehs I. Inhaled nitric oxide versus inhaled prostacyclin in acute respiratory failure in pulmonary hypertension in piglets. Pediatr Res 1995; 38: 189-204.

9. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997; 336:597-604.

10. Roberts J, Fineman J, Frederick C et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. N Eng J Med 1997; 336: 605-610.

11. UK Collaborative ECMO Trial Group: UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet 1996; 384: 75-82.

12. Obu-Osba YK, Galal O, Mansra K et al. Treatment of severe pulmonary hypertension of the newborn with magnesium sulphate. Arch Dis Child 1992; 67:31-35.

13. Tolsa J, Cotting J, Sekarski N et al. Magnesium sulphate as an alternative and safe treatment for severe persistent pulmonary hypertension of the newborn. Arch Dis Child 1995; 72: F184-F187.

14. Wu, Tzong J, Teng R et al. Persistent pulmonary hypertension of the newborn treated with magnesium sulphate in premature neonates. Pediatrics 1995; 96:472-475.

15. Bland M. Introduction to medical statistics, 3rd ed. Oxford University Press, 2000. pp 156-183.

16. Gothberg S, Edberg K, Tang S et al. Residual pulmonary hypertension in children after treatment with inhaled nitric oxide: a follow up study regarding cardiopulmonary and neurological symptoms. Acta Paediatr 2000; 89:1414-1419.

17. Kinsella JP, Abman SH. Inhaled nitric oxide: current and future uses in neonates. Semin Perinatol 2000; 24: 387-395.18. Lipkin PH, Davidson D, Spivak L et al. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. J Pediatr 2002; 140: 306-310.

19. Weimann J, Ullrich R, Hormi J et al. Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension. Anaesthesiology 2000; 90:1702-1712.

20. Weinberger B, Weiss K, Heck DE et al. Pharmacologic therapy of persistent pulmonary hypertension of the newborn. Pharmacol Ther 2001; 89: 67-79.21. Hintz SR, Suttner DM, Sheehan AM et al. Decreased use of neonatal ECMO: How new treatment modalities have affected ECMO utilization. Pediatrics 2000; 106: 1339-1343.