Treatment of severe persistent pulmonary hypertension of the newborn with magnesium sulphate

Yousef K Abu-Osba, Omar Galal, Khader Manasra, Abdellatif Rej jal

Abstract
Eight of nine newborn infants with severe persistent pulmonary hypertension of the newborn (PPHN), and a predicted mortality of 100%, and one infant with a predicted mortality >94% based on alveolar–arterial oxygen tension difference ((A–a)Do2) were treated with magnesium sulphate (MgSO4) as a life saving therapy after they failed to improve with conventional treatment. Magnesium at high serum concentrations decreases pulmonary pressures and is a muscle relaxant and sedative. Diluted MgSO4, 7H2O solution (200 mg/kg) was given intravenously over 20–30 minutes. No changes in the treatment were made after MgSO4. Mean serum magnesium concentration was maintained between 2.88 and 5.67 mmol/l by continuous intravenous infusion (six infants). Baseline arterial oxygen tension (PaO2) and haemoglobin oxygen saturation had mean (SD) values of 4–66 (1–8) kPa and 60–4 (29–7)% respectively, which started to increase one hour after MgSO4 infusion, and increased significantly at six hours to 12:04 (7–07) kPa and 91–8 (10–88)% respectively. Arterial carbon dioxide tension (PaCO2) decreased and pH increased significantly after one hour compared with the baseline value. PaO2 increases are probably secondary to a decrease in pulmonary vascular resistance and pressure, decrease in a right to left shunt, better ventilation/perfusion ratio, and PaCO2 decrease and pH rise. Seven infants survived (77–8%). These results demonstrate the beneficial effect of magnesium in the management of PPHN when other accepted treatment fails, is contraindicated, or not available.

Persistent pulmonary hypertension of the newborn (PPHN) is characterised by a suprasystemic pulmonary vascular resistance and pressure causing a right to left shunt, and marked hypoxaemia and acidosis which may produce further pulmonary vasoconstriction. In severe cases mortality rate is changing with time and ranges from 10% to 60% despite aggressive management.1–5 Infants with an alveolar–arterial oxygen tension difference ((A–a)Do2) more than 82–7 kPa (620 mm Hg) have been reported to have 100% mortality, and those with (A–a)Do2 >81–3 kPa (610 mm Hg) for eight hours 80% mortality.4,6

PPHN has a wide aetiological diversity which means that no single treatment may be uniformly effective.1–12 Mechanical hyperventilation, high frequency oscillatory ventilation, vasodilators such as tolazoline and prostaglandins, muscle relaxants, and sedatives have all been advocated.1–12 Extracorporeal membrane oxygenation has been used to treat severe cases of PPHN with various success,3 6 7–11 12 but is not available in most neonatal centres. To date no controlled studies have been performed objectively to test the efficacy of the various treatments.

At high serum concentrations magnesium is a potent vasodilator, muscle relaxant, and sedative.13–16 Previous studies showed that magnesium can prevent and reduce hypoxia induced pulmonary hypertension.17–19 Eight infants with severe PPHN and a predicted mortality of 100% and one infant with a predicted mortality >94% based on (A–a)Do2 criteria were treated with magnesium sulphate (MgSO4) as a life saving therapy after they failed to improve with conventional treatment when extracorporeal oxygenation and oscillatory ventilation were not available.

Methods and subjects
In our unit, newborn infants with PPHN are treated by conventional methods.1–4 20 Nine infants with a clinical and laboratory picture consistent with PPHN1–3 20 failed to improve with conventional management after a period ranging from 15 to 92 hours (tables 1 and 2). Congenital heart disease was excluded in all infants by echocardiography. (A–a)Do2 was greater than 84–3 kPa (630 mm Hg) in eight of nine infants, and was 82–1 kPa (616 mm Hg) in one infant (table 3). By published criteria all were considered candidates for extracorporeal membrane oxygenation.6 12 (A–a)Do2 was calculated using the following formulas:

(A–a)Do2 (kPa)=101·33×FiO2–Paco2+Pao2+6·27

(A–a)Do2 (mm Hg)=760×FiO2–(Paco2+Pao2+47)4–6

(Where FiO2 is fractional inspiratory oxygen, Pco2 is carbon dioxide tension, and Pao2 is arterial oxygen tension.)

Clinical characteristics of these infants are described in table 1. All infants had normal serum magnesium, urea nitrogen, and creatinine values. Initial treatment is summarised in table 2, and the clinical and laboratory values for individual infants before MgSO4 treatment (baseline) is presented in table 3.

Magnesium sulphate heptahydrate (MgSO4, 7H2O from Abbott Laboratories) was given as compassionate treatment. Approved hospital procedures for compassionate treatment were

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followed. Each individual case was discussed by at least two neonatologists, approved by the chairman of the department, and informed consent from the parents was then obtained. Each gram of MgSO4 7H2O contains 4.06 mmol magnesium. MgSO4 50% was diluted to 8% concentration in 5% dextrose solution. An average bolus dose of MgSO4, 200 mg/kg body weight, was given intravenously over 20–30 minutes; one infant received the bolus dose intramuscularly. A continuous intravenous drip of MgSO4 20–50 mg/kg/hour was given with the same solution for six infants. Prostaglandin E2 (PGE2), tolazoline, and pancuronium were discontinued before MgSO4 was given. No other medications or changes in the ventilator settings or FiO2 were made after MgSO4 was given except when Pao2 rose to high values; FiO2 and ventilator settings were then reduced. Blood gases, magnesium, calcium, electrolytes, and vital signs were measured before MgSO4 was given and periodically thereafter. Arterial blood gases were measured from samples drawn from the umbilical artery (postductal) with a Corning blood gas analyser, and (A–a)DO2 was calculated.

Results are given as mean (SD) for all infants unless indicated otherwise. One sample paired t test was used to compare values two hours before MgSO4 infusion and at various intervals after infusion, with the baseline values measured directly before MgSO4 infusion. Percentage change was calculated as the difference between the value at a certain interval and the baseline value, divided by the baseline value, and multiplied by 100. The χ2 test with Yates’ correction, Fisher’s exact test, two tailed test and confidence intervals were used to compare rates. Kruskal-Wallis one way analysis by ranks was used when appropriate.

Results
Serum magnesium concentration increased significantly 1 hour after the supplement, giving values of mean (SD) from 0.7 (0.1) mmol/l to 4.0 (2.2) mmol/l (p<0.01). Mean magnesium values during the first 8 hours varied from 2.88 to 5.67 mmol/l.

Umbilical arterial blood Pao2 for the individual infants and the mean for all at the various intervals are shown in fig 1. For arterial blood gases, the mean percentage change from the baseline and 95% confidence intervals (CI) are shown in fig 2. The mean (SD) of the value for Pao2 2 hours before MgSO4 infusion was similar to that at the baseline, being 5.47 (2.49) and 4.66 (1.80) kPa respectively (p<0.459). Pao2 started to increase within 1 hour after MgSO4 to

<p>| Table 1 Clinical characteristics, diagnosis, and complications before MgSO4 treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient No</th>
<th>Gestation (weeks)</th>
<th>Birth weight (g)</th>
<th>Outcome</th>
<th>Diagnosis and complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>2850</td>
<td>Survived</td>
<td>Diaphragmatic hernia, pulmonary haemorrhage, pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>3400</td>
<td>Survived</td>
<td>Perinatal asphyxia, MAS, cephalohematoma, pneumonia</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>2580</td>
<td>Survived</td>
<td>Perinatal asphyxia, MAS, SGA, sepsis, pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>3500</td>
<td>Survived</td>
<td>Perinatal asphyxia, MAS, pneumonia</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>2240</td>
<td>Survived</td>
<td>Perinatal asphyxia, HMD, polycythemia, probable sepsis</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>2400</td>
<td>Died</td>
<td>Perinatal asphyxia, probable sepsis, gastric and pulmonary haemorrhage</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>2880</td>
<td>Died</td>
<td>Perinatal asphyxia, MAS, pneumonia</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>1770</td>
<td>Survived</td>
<td>Perinatal asphyxia, intracranial bleed, seizures, bilateral pneumothorax</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>2450</td>
<td>Survived</td>
<td>Diaphragmatic hernia, cleft lip and palate, SGA, pneumonia</td>
</tr>
</tbody>
</table>

MAS, meconium aspiration syndrome; SGA, small for gestation; HMD, hyaline membrane disease.

Table 2 Summary of treatment, ventilator settings, and duration before MgSO4 treatment

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Drugs</th>
<th>Mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tolazoline</td>
<td>PGE2</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

PIP, positive inspiratory pressure; PEEP, positive end expiratory pressure; FiO2, fractional inspiratory oxygen pressure.

Table 3 Initial clinical and laboratory values for individual infants before MgSO4 treatment. Mean blood pressure values are shown

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Serum magnesium (mmol/l)</th>
<th>Rate (bpmm)</th>
<th>Blood pressure (mm Hg)</th>
<th>Pao2 (kPa)</th>
<th>Pao2 (kPa)</th>
<th>Oxygen saturation (%)</th>
<th>(A–a)DO2 (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.64</td>
<td>154</td>
<td>7.47</td>
<td>5.87</td>
<td>4.27</td>
<td>67</td>
<td>84.93</td>
</tr>
<tr>
<td>2</td>
<td>0.68</td>
<td>141</td>
<td>7.35</td>
<td>5.27</td>
<td>1.87</td>
<td>12</td>
<td>82.13</td>
</tr>
<tr>
<td>3</td>
<td>0.64</td>
<td>136</td>
<td>7.56</td>
<td>3.33</td>
<td>6.93</td>
<td>92</td>
<td>84.80</td>
</tr>
<tr>
<td>4</td>
<td>0.94</td>
<td>150</td>
<td>7.15</td>
<td>6.27</td>
<td>1.87</td>
<td>12</td>
<td>82.13</td>
</tr>
<tr>
<td>5</td>
<td>0.68</td>
<td>147</td>
<td>7.38</td>
<td>4.53</td>
<td>6.0</td>
<td>81</td>
<td>84.53</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>171</td>
<td>7.08</td>
<td>7.33</td>
<td>2.27</td>
<td>13</td>
<td>85.47</td>
</tr>
<tr>
<td>7</td>
<td>0.58</td>
<td>120</td>
<td>7.42</td>
<td>2.46</td>
<td>6.67</td>
<td>73</td>
<td>87.60</td>
</tr>
<tr>
<td>8</td>
<td>0.68</td>
<td>148</td>
<td>7.19</td>
<td>4.93</td>
<td>6.4</td>
<td>75</td>
<td>83.73</td>
</tr>
<tr>
<td>9</td>
<td>0.65</td>
<td>134</td>
<td>7.51</td>
<td>4.40</td>
<td>5.73</td>
<td>84</td>
<td>84.93</td>
</tr>
<tr>
<td>Mean</td>
<td>0.7</td>
<td>144</td>
<td>7.35</td>
<td>4.90</td>
<td>6.60</td>
<td>64</td>
<td>84.97</td>
</tr>
</tbody>
</table>

SD 0.11 14.3 15.66 0.17 1.43 1.8 29.7 1.47

Figure 1 Pao2 changes before and after MgSO4 treatment for individual infants. Each line represents one infant, the mean for all the infants treated is shown as wide solid line with solid circles.
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Figure 2. Mean and 95% confidence intervals of percentage change in the arterial blood gas values before and after MgSO4 treatment for all infants.

11-29 (11-41) kPa (p<0.137), mean percentage change was 181-4% and CI was -45-65 to 408-49. At 2 and 4 hours, PaO2 showed a trend to be higher than baseline (p<0.12 and p<0.06 respectively). PaO2 was significantly higher at 6 and 8 hours, with values at 12-04 (7-07) kPa (p<0.029) and 16-47 (12-63) kPa (p<0.035) respectively, and percentage mean change (and CI) from the baseline of 203% (26 to 379%) and 294% (6 to 582%) respectively. Kruskal-Wallis one way analysis by ranks showed that PaO2 had changed significantly during the study period (p<0.004).

Mean (SD) haemoglobin oxygen saturation at 2 hours before MgSO4 infusion was similar to baseline (64 (27)% and 60 (30)% respectively; p<0.78). Saturation increased significantly within 1 hour after MgSO4 infusion to 84 (18)% (p<0.017) and at 8 hours to 95 (6)% (p<0.02). Percentage change (and CI) were 130% (-27 and 288%) and 119% (-87 to 325%) respectively.

PaCO2 means (SD) were similar at 2 hours before MgSO4 and at the baseline (4-75 (0-89) and 4-9 (1-43) kPa respectively), and decreased to 4-07 (0-78) kPa (p<0.048) and 3-29 (0-89) kPa (p<0.04) at 1 and 8 hours respectively, mean percentage change and CI being shown in fig 2. Mean (SD) values of arterial pH at 2 hours before MgSO4 infusion and the baseline were 7-37 (0-1) and 7-35 (0-17). Arterial blood pH showed a significant increase at 1, 2, and 4 hours after infusion (p<0.034, p<0.046 and p<0.045) and showed a trend to be higher at 6 and 8 hours, p<0.066 and p<0.08 respectively, mean percentage change and CI being shown in fig 2. Comparing bicarbonate and base excess values during the study period and the baseline did not reveal significant changes. Means (SD) of arterial blood bicarbonate 2 hours before MgSO4 at the baseline and after 8 hours were 20-5 (5-6), 20-1 (6-9), 20-4 (4-6).

(A-a)DO2 started to decrease from the baseline (85 (1-5) kPa) within 1 hour after MgSO4 (80 (1-1) kPa, p<0.09) and was significantly lower after 8 hours 72-2 (13-2) kPa, p<0.025, mean percentage change and CI being shown in fig 2. Seven infants (77-8%) survived while on treatment; in the two infants who died a small decrease in (A-a)DO2 was seen initially but it remained greater than 82-67 kPa (620 mm Hg) until they died. One infant died seven days after stopping MgSO4 treatment. None of the infants who died responded to tolazoline and dopamine treatment.

Heart rate 2 hours before MgSO4 was similar to the baseline value: means (SD) were 142 (22) and 145 (14) beats/minute (bpm) respectively. Heart rate showed a trend to decrease during the study period. After 1 and 8 hours the heart rate was 143 (12) bpm (p<0.66) and 129 (14) bpm (p<0.089), but not below 116 bpm in any surviving infant during the study period.

Baseline mean blood pressure for all infants was similar to that at 2 hours before MgSO4 infusion, the values being 54-2 (15-7) and 54 (13-6) mm Hg respectively. Although mean blood pressure showed a trend to decrease at 2 hours after MgSO4 infusion to 47-1 (15-1) mm Hg (p<0.08), it did not show any significant change during the 8 hour period. At 8 hours blood pressure was 51-4 (11-8) mm Hg. No significant changes were observed during the study period in the serum electrolytes and calcium.

Ultrasound scans were taken of the head in all infants and none developed intracranial haemorrhage during treatment. Patient 8 who had had severe perinatal asphyxia and had been successfully resuscitated from a cardiac arrest at 2 days of age, before MgSO4 treatment, had an intraventricular haemorrhage and subsequently developed hydrocephalus. Patient 4 had normal head scans before and at two and seven days after treatment but showed an old infarct lesion in the left frontal lobe in a follow up computed tomographic scan of the brain one month after the treatment. Patient 3 subsequently developed bronchopulmonary dysplasia. No infant had any bleeding from gastrointestinal and urinary tract or through the endotracheal tube during the study period.

Discussion

Drugs that are specific pulmonary vasodilators and reduce pulmonary hypertension are not available yet for clinical use. Pulmonary vasoconstriction depends on the availability of calcium to the affected cells,21 22 and therefore
calcium channel blockers have been tried to induce pulmonary vasodilatation. Magnesium is nature’s calcium antagonist: it is a muscle relaxant, vasodilator, sedative, and antithrombotic. 13 14 23–29 Cropp showed in dogs that increase in blood magnesium to 5–6 mmol/l will bring hypoxic pulmonary vasoconstriction without causing deleterious changes in haemodynamics or pulmonary ventilation. 20 Paidas showed that continuous infusion of ATP and magnesium chloride produced a significant decrease in mean pulmonary artery pressure after induced hypoxia, but magnesium chloride had no effect when infused alone; 18 but the doses given were very small and magnesium chloride values in the blood were not measured. Abu-Osba et al showed in anaesthetised sheep that a sharp increase in the mean pulmonary artery pressure occurred by breathing 10% oxygen, but during hypoxia it fell suddenly to the baseline after MgSO4 infusion. 19 No significant change in the cardiac output was observed, and the heart rate decreased transiently. In contrast, no change was observed after placebo infusion. Magnesium aspartate hydrochloride oral therapy has been shown by Mathew et al to attenuate monocrotaline induced pulmonary hypertension, right ventricular hypertrophy and pathological changes in the pulmonary vasculature in rats. 30 Howel and Carrier showed that in rabbit, magnesium reduces the contractile responses of the pulmonary artery to noradrenaline and histamine and alters the sensitivity to histamine. 31 These studies demonstrate the beneficial effect of magnesium in reducing pulmonary hypertension.

MgSO4 has been used for several decades to treat toxaemia of pregnancy. During treatment maternal serum magnesium concentration is 2–3.5 mmol/l and magnesium ions cross the placenta promptly to achieve equilibrium between the mother and the fetus. 26 Side effects of hypermagnesaemia, which has beneficial therapeutic applications in infants with PPHN, include: central nervous system depression, hyporeflexia, and decreased excitability. 27 28 32 33 Possible undesirable side effects include calcium and potassium disturbances. 27 28 34 Frequent monitoring of blood concentrations and appropriate supplantations will prevent these complications. Abdominal distension may occur, with absence of bowel sounds. Infants with PPHN usually have a gastric tube inserted and connected to low pressure suction or free drainage and usually they are not fed enterally. High serum concentrations of magnesium may produce respiratory depression, a non-consequential effect in these mechanically ventilated infants. The MgSO4 dose we used and the serum values were similar to that used in toxaemia of pregnancy which has been proved to be safe for both the fetus and the newborn infant. 20–28 52

Ideally, a controlled double blind study should have been done to test the efficacy and safety of this treatment. Our study was not controlled and our justification was that all the infants were treated with MgSO4 on a compassionate basis after all other available treatment had failed to relieve the severe hypoxaemia and they were expected to die (according to the accepted criteria of (A–a)Do2 used in various studies). There are no pilot studies in humans showing that MgSO4 can treat PPHN, although there is good theoretical and experimental evidence to support this. As the incidence of PPHN is very low it will require a long period to conduct a randomised controlled study unless a multicentre study is organised.

Carter et al reported 22 of 25 patients survived (88%) with (A–a)Do2 $\geq$ 80 kPa (600 mm Hg); they required extracorporeal membrane oxygenation treatment after failure of high frequency oscillatory ventilation and conventional therapy. 3 Dwoertz et al reported survival rates in patients eligible for extracorporeal membrane oxygenation based on (A–a)Do2 $\geq$ 81.33 kPa (610 mm Hg) for eight hours with a predicted mortality 80%. 2 In 1980–1 survival rate was 0% (0/5) and 1986–8 survival rate was 89% (8/9). Although our patients were severely ill, with (A–a)Do2 $\geq$ 82.67 kPa (620 mm Hg) in eight patients (predicted mortality 100%), and 82–13 kPa (616 mm Hg) in one patient (predicted mortality 94%), the survival rate in our study was 77.8% (7/9), which is comparable with Carter et al and Dwoertz et al. 7

Though we did not measure the pulmonary pressure, we suggest that the observed increase in PaO2 and haemoglobin oxygen saturation is probably secondary to the vasodilator effect of magnesium on the pulmonary vessels. The relief of hypoxaemia, the continuing effect of magnesium, muscle paralysis, and the expected improvement in ventilation: perfusion ratio, could be reasons for PaCO2 decreases and pH increases which then lead to further improvement in oxygenation.

Several prostaglandins have been used to decrease pulmonary hypertension. 5–10 MgSO4 has a powerful effect on the production and release of several prostaglandins, especially PG12 and its metabolite 6-keto-PGF1α, Nadler and Hennicke 4 show that magnesium acts on smooth muscle relaxation; it has a hypotensive effect, decreases the sensitivity to hypoxia, and decreases excitability. 27 28 32 33 Possible undesirable side effects include calcium and potassium disturbances. 27 28 34 Frequent monitoring of blood concentrations and appropriate supplantations will prevent these complications. Abdominal distension may occur, with absence of bowel sounds. Infants with PPHN usually have a gastric tube inserted and connected to low pressure suction or free drainage and usually they are not fed enterally. High serum concentrations of magnesium may produce respiratory depression, a non-consequential effect in these mechanically ventilated infants. The MgSO4 dose we used and the serum values were similar to that used in toxaemia of pregnancy which has been proved to be safe for both the fetus and the newborn infant. 20–28 52

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sites of prostaglandins. Some reports describe a beneficial magnesium vasodilator effect and reduction of complications after ischaemic hypoxia in the central nervous system, in ischaemic heart disease, and in kidney and liver conditions which frequently coexist with PPHN in the severely hypoxaemic neonate. This study and others suggest the possible benefits of magnesium treatment in PPHN when conventional therapy fails and alternative modes of therapy, for example, extracorporeal membrane oxygenation and high frequency oscillatory ventilation are not available or are contraindicated. A controlled multicentre study is required before recommending magnesium as primary treatment and further work is needed to clarify its mechanism of action in PPHN. Close monitoring of blood pressure, kidney function, electrolytes, glucose, and calcium should be observed and long term follow up is needed.

We thank Professor RDG Milner for his critical review of the manuscript.