

# Role of magnesium sulphate in treatment of severe persistent pulmonary hypertension of the newborn

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## ABSTRACT

**Objective:** Treatment of severe persistent pulmonary hypertension of the newborn remains controversial and various modalities of treatment have been tried. This study was performed to evaluate the effect of magnesium sulphate (MgSO<sub>4</sub>) as a treatment of persistent pulmonary hypertension of the newborn (PPHN) in full term babies.

**Methods:** This study was carried out in the Maternity and Children's Hospital, Jeddah, Kingdom of Saudi Arabia from January 1998 to 2000. A non-randomized study in 8 newborn babies who were admitted to the Intensive Care Unit and diagnosis of PPHN based on echocardiogram was conducted to assess the efficacy of MgSO<sub>4</sub> 8% dilution in a loading dose of 200mg/kg followed by a maintenance dose of 20-100mg/kg/hour. No other vasodilators were

given, patients were not hyperventilated. The aim was to keep magnesium levels 3.5-5.5mgmmol/l.

**Results:** Seven out of 8 patients showed marked improvement in partial pressure oxygen at 6 hours and maximum improvement at 24 hours. The same improvement noticed in peak inspiratory pressure, and ventilatory time support.

**Conclusion:** Results suggests that MgSO<sub>4</sub> may be considered as an alternative treatment in PPHN when no other modalities are available as it is a non aggressive and low cost treatment.

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**P**ersistent pulmonary hypertension of the newborn (PPHN) can be defined as failure of the normal postnatal fall in pulmonary vascular resistance which leads to persisting right to left shunt across the fetal channels (Foramen ovale [PFo], patent ductus arteriosus [PDA], intrapulmonary vessels). Although PPHN is not a common condition, it carries a high mortality. It can be primary or secondary. Primary is a form of the disease, which typically presents soon after birth with hypoxemia in a baby with clinically and radiologically normal lungs. It is usually associated with complications of pregnancy as diabetes mellitus, hypertension, maternal iodomethacin ingestion. Secondary PPHN occurs

due to a disease in the lung parenchyma such as meconium aspiration syndrome (MAS), severe pneumonia, hyaline membrane disease, diaphragmatic hernia, and pulmonary hypoplasia. The pathophysiology of the disease is pulmonary vasoconstriction, which leads to failure of the pulmonary vascular resistance to decrease and remains equal or greater than systemic vascular resistance. Diagnosis is made by lability of oxygenation, difference between pre and post ductal partial pressure oxygen (PaO<sub>2</sub>) 20 mm Hg, and echocardiogram (to exclude congenital heart disease (CHD) and define pulmonary artery pressure). Treatment remains controversial and various

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modalities of treatment have been tried including; hyperventilation with sedation, muscle relaxants, vasodilators, high frequency oscillatory ventilation (HFOV), extra corporeal membrane oxygenation (ECMO), and nitric oxide. Magnesium sulphate (MgSO<sub>4</sub>) has been used for many decades to treat toxemia of pregnancy which is a natural calcium antagonist acting on the metabolism of prostaglandin, suppression of the release of catecholamines, reduce the responsiveness of smooth muscles to vasopressors.<sup>1-3</sup> These studies showed that MgSO<sub>4</sub> at high concentration is a potent vasodilator and can prevent and reduce hypoxia induced PPHN, sedative, muscle relaxant and has an antithrombotic effect on the brain and kidney. These results are comparable to our study.

**Methods.** A clinical prospective non randomized study in the Maternity and Children's Hospital, Jeddah, Kingdom of Saudi Arabia, from January 1998 to 2000 was carried out on 8 newborn babies who were admitted consecutively to Neonatal Intensive Care Unit (NICU) with profound hypoxia and respiratory failure due to PPHN. All babies were on conventional type of ventilation. The diagnosis was based on persistent profound hypoxemia (PaO<sub>2</sub> ≤ 50 mm Hg). Lability of oxygenation with great variation in PaO<sub>2</sub> without changes in ventilator setting. All infants had alveolar arterial oxygen differences (A-a DO<sub>2</sub>) of 600 mm Hg and confirmed the diagnosis by echocardiography to exclude case of CHD. The group consisted of one female and 7 males. **Table 1** shows their clinical characteristic and their gestational age which were between 38-41 years (mean standard deviation [SD] 39.1). The minimum weight was 2.680kg and the maximum was 4.2kg. The following parameters

reassessed (A-aDO<sub>2</sub>) by using the formula = (A-DO<sub>2</sub> mm Hg) = 760 x fractional inspired oxygen (FiO<sub>2</sub>) - (PaO<sub>2</sub> + partial pressure carbon dioxide [PCO<sub>2</sub>] mm Hg + 47), PaO<sub>2</sub> (mm Hg), peek inspiratory pressure (PIP) (cm water [H<sub>2</sub>O]) and ventilatory time support. All patients were given the appropriate ventilatory support and the routinely supportive management including volume expanders at a rate of 20-30ml/kg, dopamine if needed and sedation with pethidine. Appropriate ventilatory support before and during MgSO<sub>4</sub> treatment the following were monitored: Vital sign (heart rate, blood pressure, temperature, respiratory rate) every 2-4 hours. Ventilator settings (FiO<sub>2</sub>, PIP, peak end expiratory pressure [PEEP], mean airway pressure [MAP]) at 2 hours interval and then every 4-6 hours, arterial blood gases (pH, PCO<sub>2</sub>, PaO<sub>2</sub>) every 2 hours in the first 12 hours and then every 6 hours. Measurements of blood gases were obtained through an indwelling umbilical arterial catheter (size 5.5 french gauge). Magnesium (Mg) level before and then every 12 hours during the MgSO<sub>4</sub> treatment, which the blood chemistry was measured every 12 hours. All results and variable are expressed as mean standard deviation. The initial ventilatory setting was as follow: FiO<sub>2</sub> 100%, PIP 30cm H<sub>2</sub>O, PEEP 4cm H<sub>2</sub>O, MAP 17cm H<sub>2</sub>O. Magnesium sulphate was started at a postnatal age, minimum of 6 hours at a Bolus dose of MgSO<sub>4</sub> 200mg/kg diluted from 10-8% over 30 minutes. A continuous infusion by intravenous drip of 20-100mg/kg/hour was then given from the same solution. Magnesium sulphate maintenance dose was ranging between 20-100mg/kg/hour. The mean MgSO<sub>4</sub> dose needed was 50mg/kg/hr. Case number one, 2 the dose needed was 50mg/kg/hr and the treatment was reduced gradually by 10mg/kg/hr over 48 hours. Case 3, 4, 5 MgSO<sub>4</sub> needed was 30mg/kg/

**Table 1** - Clinical characteristics of newborn babies (n=8).

Patient	Gestational (weeks)	Sex	Birth Weight (kg)	A/S 1, 5 (min)	Mode of delivery	Diagnosis
1	40	Male	3500	5, 8	SVD	Birth asphyxia, MAS, PPHN, pneumothorax
2	40	Male	3100	3, 6	LSCS	Birth asphyxia, mec. asp.
3	41	Female	2680	2, 6, 8	SVD	Severe birth asphyxia, MAS, sepsis + GBS pneumonia
4	40	Male	3100	6, 8	LSCS	Birth asphyxia, MAS, <i>staphylococcus aureus pneumoniae</i>
5	38	Male	4200	7, 8	SVD	IDM, severe mec. asp., PPHN
6	39	Male	3200	9, 10	SVD	Severe pneumonia, <i>klebsiella</i> bilateral pneumothorax
7	40	Male	3500	5, 8	SVD	Idiopathic
8	40	Male	3700	2, 4	LSCS	Birth asphyxia, severe meconium aspiration, PPHN

A/S - Apgar score, SVD - spontaneous vaginal delivery, MAS - meconium aspiration syndrome, PPHN - persistent pulmonary hypertension of the newborn, LSCS - lower segment cesarean section, GBS - Group B streptococcal, IDM - infant of diabetic mother, mec. asp. - meconium aspiration, n - number

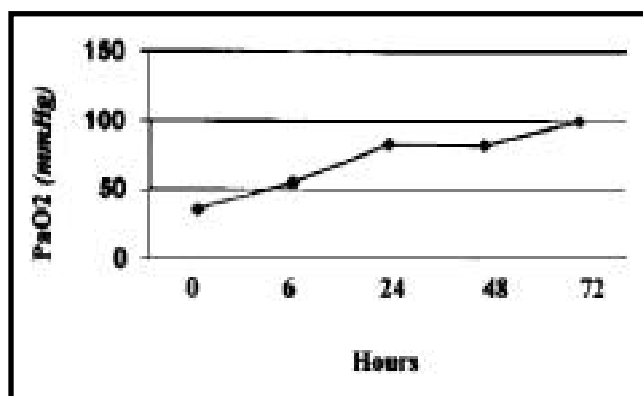
hr and reduced gradually over 72 hours. Case 6, 7, 8 the dose was 40mg/kg/hr and treatment was reduced over 100 hours. The aim was to obtain a blood concentration between 3.5-5.5mmol/L (7-1mg/dl). No other medication was given. All babies were followed for the first week of life (120 hours) during MgSO<sub>4</sub> treatment until the time of extubation. Once the PaO<sub>2</sub> stabilized, ventilator setting was reduced – MgSO<sub>4</sub> is then reduced gradually by 10mg/kg/hour.

Data for all cases were analyzed using a Statistical Package for Social Sciences (SPSS) program. Frequency tables with mean values of various measurements and standard deviation were produced. Student's tests were applied to determine significant differences between mean. Significance level was set on value of 0.05.

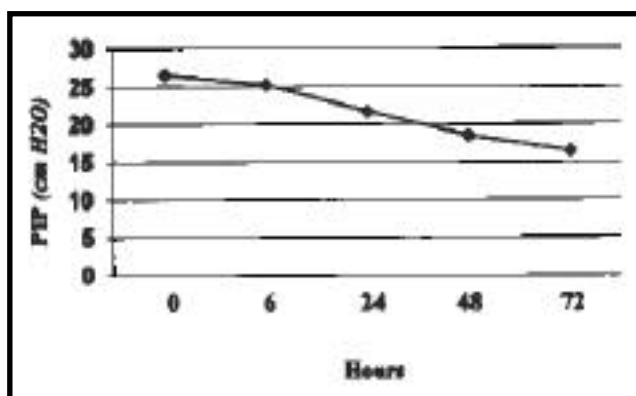
**Results.** The blood Mg concentration of all cases increased in the first 6 hours to reach a mean of 9mg/dl maintained between 7-11mg/dl. No hypocalcemia was noted. Mean duration of treatment in hours was 78 hours with minimum of 48 hours and maximum of 120 hours. Improvement was noted of pH and PCO<sub>2</sub> which reached gradually maximum at 6 hours after MgSO<sub>4</sub> started. Baseline arterial oxygen tension (PaO<sub>2</sub>) had mean values of 37.4 mm Hg which started to increase significantly at 6 and 24 hours to mean (88.2) mm Hg and 94 mm Hg. The P values <0.001 and <0.0001 (**Figure 1**) (A-a DO<sub>2</sub>) has significantly decreased from mean 619-510mm Hg in the first 24-48 hours. (P value 0.003) Peak inspiratory pressure has also significantly reduced from mean 30.4cm H<sub>2</sub>O to 24cm H<sub>2</sub>O, 18cm H<sub>2</sub>O at 24, 48 hours, P values <0.001 and <0.0001 (**Figure 2**). Mean ventilatory time for all infants was 11.8 days with a minimum of 5 and maximum of 20 days. There was no adverse effect noted by Mg management such as hypotension or bradycardia and all babies showed normal serum electrolytes level.

Seven out of the 8 babies survived, one died from severe birth asphyxia with intraventricular hemorrhage (IVH) proved by computerized tomography (CT) scan. After treatment all infants were followed for the first year of life. All have normal neurological examination, with normal visual and hearing tests, normal brain ultrasound and brain CT scan. Only one infant developed chronic lung disease (n=8).

**Discussion.** Persistent pulmonary hypertension of the newborn remains one of the fatal diseases and treatment still remains controversial. Various modalities of treatment include: Hyperventilation, paralysis, inotropic support, alkalisation and vasodilators. Tolazoline was the most widely used vasodilator but has significant side effect including systemic hypotension gastric bleeding. Extra corporal membrane oxygenation has been used with varying success. Recently, inhalation of nitric oxide has received much attention and several studies reported successful and better outcome in most of the centers.<sup>4-5</sup> Infants with alveolar-arterial oxygen difference 620 mm Hg have been reported to have 100% mortality. Vasoconstriction is calcium dependent. Magnesium is a natural calcium antagonist, it causes suppression of prostaglandin metabolism. Animal studies showed that increasing Mg has a sedative, muscle relaxant, antithrombotic effect.<sup>6-10</sup> Magnesium sulphate has been used for many decades to treat toxemia of pregnancy. During treatment maternal serum Mg concentration is 2-3mmol/L and Mg ions cross the placenta to achieve equilibrium between fetus and mother.<sup>11</sup> Side effect of hypermagnesemia which has beneficial effects in infants with PPHN include: cerebral sedation, muscle relaxant, hyporeflexia and decreased excitability. Some reports describe a beneficial Mg vasodilator effect and reduction of complications after ischemic



**Figure 1** - Mean pressure arterial oxygen (mm Hg in relation to hours of treatment). Hours - pressure arterial oxygen (mm Hg), 0=37.2, 6=52, 24=82, 48=88.2, 72=94. PaO<sub>2</sub> - pressure arterial oxygen.



**Figure 2** - Mean peak inspiratory pressure (cm H<sub>2</sub>O) in relation to hours of treatment. Hours - peak inspiratory pressure, 0=28, 6=25, 24=24, 48=18, 72=16, PIP - peak inspiratory pressure.

hypoxia in the central nervous system.<sup>9-14</sup> Since 1995, many studies have been carried out to demonstrate the efficacy of MgSO<sub>4</sub> and most of these studies showed a good outcome.<sup>6-10</sup> In this study, all cases presented with severe PPHN all showed good and marked improvement in PO<sub>2</sub> and decrease in ventilatory setting at 6 hours and 24 hours. Also there was a decrease in total oxygen depending time. There was no associated biochemical abnormality, and patient survival was complete except one who died as of the sequelae of severe birth asphyxia.

In conclusion, this report provides evidence that Mg play a role in the treatment of PPHN. It is a non-aggressive treatment of short duration and low cost. Further studies to confirm this and to investigate regarding long term side effects are needed in the future and also to strongly suggest the use of MgSO<sub>4</sub> as an alternative treatment when other treatment modalities are not available.

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