*Original article*

# MAGNESIUM SULPHATE AS A SAFE TREATMENT FOR PERSISTENT PULMONARY HYPERTENSION OF NEWBORN RESISTANT TO MECHANICAL HYPERVENTILATION

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**ABSTRACT**

***Objective:*** To see the effects of magnesium sulphate in newborn with persistent pulmonary hypertension of newborn (PPHN) who did not respond to mechanical hyperventilation and are candidate for Extra Corporeal Membrane Oxygenation (ECMO).

***Methodology***: Ten newborn who were admitted to Neonatal Intensive Care Unit (NICU) with profound hypoxia and respiratory failure due to PPHN were treated with conventional mechanical ventilation and then mechanical hyperventilation. The newborns who did not respond to mechanical Hyperventilation were treated with magnesium sulphate infusion.

***Results:*** Nine out of ten babies survived and one of them died. The differences between the mean AaDo2, OI index, and PH after mechanical hyperventilation and magnesium sulphate administration was significant.

***Conclusions:*** Magnesium has a role in the treatment of PPHN patients who do not respond to hyperventilation or may be applied instead of hyperventilation.

**KEY WORDS:** Persistent pulmonary hypertension newborn, Magnesium sulphate, Mechanical hyperventilation, Oxygen index, Alveolar-arterial oxygen differences.

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## INTRODUCTION

Failure to achieve or sustain the normal decrease in pulmonary vascular resistance at birth, leading to right to left shunt across the fetal channels, severe respiratory distress and hypoxia, are referred to as persistent pulmonary hypertension of newborn (PPHN). Various treatment modalities have been used to treat this.

Newer type of treatment including inhaled nitric oxide and ECMO have been recommended in the treatment of PPHN, which are not available in many of the developing countries including Islamic republic of Iran. Though mechanical hyperventilation is still the cornerstone of treatment of PPHN, however prolong hyperventilation can lead to adverse effect on pulmonary function and neuro developmental outcome. Infusion of magnesium sulphate may have a role in the treatment of PPHN who did not respond to mechanical hyperventilation or may be employed instead of it.

In the fetus, about 87% of right ventricular output crosses the ductus arteriosus and enters the aorta, bypassing the lungs. Blood flow through the lungs is diminished because of the high resistance of the fetal pulmonary circuit, the open ductus arteriosus and the lower resistance of the systemic circuit. The high basal pulmonary vascular resistance (PVR) in fetus is related to low oxygen tension, low basal production of vasodilator products (Such as prostacyclin and nitric oxide), increased

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production of vasoconstrictors (including endothelin-1 or leukotriens), and altered smooth muscle cell reactivity (such as enhanced tone).[1-3] Coincident with clamping of the cord, the low resistance placenta is removed from the systemic circuit and systemic blood pressure rises. The rise in systemic pressure, coupled with the fall in PVR and in pulmonary artery pressure, decreases the right to left shunt through the ductus arteriosus. With ductal shunting diminished, pulmonary artery blood flow increases, resulting in increased pulmonary venous return to the left atrium and increased pressure in left atrium. Once the left atrial pressure exceed right atrial pressure, the foramen ovale closes.[4] The PPHN may be idiopathic (Primary) or secondary to hyperviscosity of blood, aspiration pneumonia specially meconium aspiration, neonatal sepsis, congenital diaphragmatic hernia, or neonatal pulmonary disease (particularly pulmonary hypoplasia, with or without diaphragmatic Hernia). The primary forms tend to occur in full term of post mature infants. The incidence of PPHN was reported to be 0.37% among neonate delivered by elective cesarean section, almost five fold higher than in those who had normal vaginal delilvery.[5] Diagnosis is made by lability of oxygenation, difference between pre and post ductal partial pressure oxygen (Pao2) > = 20 mmHg and echocardiogram (To exclude congenital heart disease and define pulmonary artery pressure). Because PPHN is a labile disease, documentation of normal arterial Pao2 at some point during the course does help exclude congenital heart disease. Various modalities of treatment including; oxygen, surfactant, inhaled nitric oxide, extra corporeal membrane oxygenation (ECMO), high frequency ventilation, respiratory alkalosis, vasodilators, Alkali infusion have been tried. Magnesium sulfate has been used to treat pulmonary hypertension of newborn.[6-8] The parameters most frequently used to predict poor outcome in infants failing conventional ventilator support and regarded as entry criteria for ECMO include oxygen index(OI)35 to 60 for 0.5 to 6 hours[9] AaDo2 605 to 620mmhg for 4 to 12 hours,[10] Pao2 35 to 50mmhg for 2 to 12 hours[11] and PH<7.25 for two hours.[12] We studied the effect of magnesium sulphate in newborn with PPHN, who did not response to hyperventilation and candidate for ECMO.

## PATIENTS AND METHODS

This is a clinical prospective, non randomized study in the neonatal intensive care unit of Imam Hospital, Ahvaz, Islamic republic of Iran, conducted from June 2005 to March 2006. It enrolled ten newborn who were admitted consecutively in neonatal intensive care unit (NICU) with profound hypoxia and respiratory failure due to PPHN. All babies were on conventional mechanical ventilation. The diagnosis was based on persistent profound hypoxemia (Pao2<50mmHg), lability of oxygenation with great variation of Pao2 before and after conventional mechanical ventilation. All patients were paralyzed with pancuronium 0.1mg/kg and hyperventilated (Respiratory rate 100/min, Peak inspiratory pressure 35cm H2O, positive end expiratory pressure 5cm H2O, oxygen concentration 100% and mean airway pressure. Umbilical artery catheterizations were performed for all patients. All newborn infants had a predicted mortality over 80% based on oxygen index. Magnesium sulphate was started at a dose of 200mg/kg over 30 minutes.

A continuous infusion by intravenous drip of 20-50 mg/kg/hour was then given from the same solution. Magnesium level was measure every two hours to maintain serum magnesium concentration between 7-11mg/dl, and then every 24 hours. The following parameters, oxygen index (OI) by using the formula=OI=100 × mean airway pressure × fio2 /postductal PaO2, Alveolar arterial oxygen differences [(A-a DO2) =711-(PaO2+ PaCO2], with respect to 758 mmHg, the barometric pressure at Ahvaz, and PH reassessed before and after conventional mechanical ventilation two hours after initiation of mechanical hyperventilation and after magnesium sulphate administration. Vital signs every 4 hours, ventilator setting, arterial blood gas every two hours and hemoglo-

bin oxygen saturation with pulse oximeter were monitored. Based on arterial blood gases, the setting of ventilator were weaned and when the ventilator support had decreased to a peak inspiratory pressure of 25cm H2O, fractional inspired oxygen of 60% and a rate of 60/minutes, the infusion of magnesium sulphate were discontinued. The newborn's age at initiation of mechanical ventilation, newborn weight, duration of mechanical ventilation, the interval of response to magnesium sulphate, duration of magnesium sulphate treatment, the days of admission and the rate of morbidity and mortality were recorded. The patients were followed for six months. Data for all cases were analyzed using a statistical package for social sciences (SPSS) program. Students T test were applied to determine significant differences between the mean. Significance level was set on value of 0.05.

## RESULTS

The blood magnesium concentration of all cases increased in the first six hours to reach a mean of nine mg/dl maintained between 7-11mg/dl. In case number 1-5 the dose needed was 35mg/kg/hr, case number 6-8, 40mg/kg/dl and case number 9-10, 50mg/kg/hr. The minimum weight was 2650gr, the maximum was 3850gr and the mean was 3195±390.47gr. The mean age of patients at initiation of mechanical ventilation was 30.8±11.839 with a minimum of 10 and maximum of 48 hours. The mean interval after infusion of magnesium sulphate to obtain a partial arterial oxygen tension>60mmHg was 5.40±2.83 with a minimum of two and maximum of 8 hours. Mean vetilatory time for all infants was 6.40 ± 1.57 with a minimum of five and maximum of nine days. The mean duration of treatment with magnesium sulphate was 3.30±1.05 with a minimum of two and maximum of five days. The mean duration of admission was 12.9±6.1 with a minimum of nine and maximum of 28 days. Nine out of ten babies survived, one died from tension pneumothorax. One of the survivor patient developed non communicating hydrocephalus at 45 days of life in which ventriculoperitoneal shunt was inserted. Three patients developed atelectasis after extubation, who were treated with chest physiotherapy and tracheal suction.

The mean of AaDO2 before hyperventilation was 628.8±909 and two hours after hyperventilation was 624.6±11.3. The differences between the means of AaDO2 was not significant (P>0.05). The mean of AaDO2 after administration of magnesium sulphate was 574.1±38.2. The differences between the means of AaDO2 after hyperventilation and magnesium sulphate administration was significant (P<0.05). The means of PH before hyperventilation was 7.09±0.21 and two hours after hy-

Table-I: Paired Samples Test (n=10)

| Paires | Mean | Std. Deviation | 95% Confidence Interval Of the Difference | | t | P.V. |
|---|---|---|---|---|---|---|
| | | | Lower | Upper | | |
| Pair 1 AaDo2 before M.H.V._ AaDo2 after M.H.V. | 4.20 | 8.829 | -2.12 | 10.52 | 1.504 | .167 |
| Pair 2 AaDo2 after M.H.V._ AaDo2 after M.S.I. | 50.50 | 37.497 | 23.68 | 77.32 | 4.259 | .002 |
| Pair 3 PH before M.H.V._ PH after M.H.V. | .0130 | .26399 | -.1758 | .2018 | .156 | .880 |
| Pair 4 PH after M.H.V. _ PH after M.S.I. | -.1530 | .17140 | -.2756 | -.0304 | -2.823 | .020 |
| Pair 5 OI after M.H.V. _ OI after M.S.I. | 49.30 | 43.904 | 17.89 | 80.71 | 3.551 | .006 |

M.H. V: Mechanical Hyperventilation AaDo2: Alveolar arterial oxygen differences
M.S.I.: Magnesium Sulphate Infusion O.I.: Oxygen Index

perventilation was 7.08±0.14 (P>0.05). The mean of PH after mg sulphate administration was 7.23±0.15 (P<0.05). The mean of OI after hyperventilation was 71.5±39.2 and after magnesium sulphate administration was 22.2±7.6 (P<0.05) (Table-I). The mean of PaCO2 two hours after hyperventilation was 50.4 Echocardiography were performed in all the patients. None of them had congenital heart disease.

## DISCUSSION

Persistent pulmonary hypertension of the newborn contributes to neonatal hypoxemia, which is often refractory and associated with a high mortality (11%-48%).[13-15] The prevalence of PPHN has been reported one per 700 live birth.[16] The optimal approach to the treatment of PPHN remain controversial. A variety of treatment modalities including hyper ventilation.[17-18] high frequency,[19] surfactant, Alkali infusion,[20] non specific vasodilators such as tolazolin,[21] prostaglandins, inhaled nitric oxide,[22] Adenosin,[23] extracorporeal membrane oxygenation (ECMO)[24] have been used. Hyperventilation (defined as a PaCO2<35mmHg for >12hours) was used in the treatment of 66% of neonates with wide variation between centers.[25] The newer types of treatment of PPHN include inhaled nitric oxide and ECMO which is not available in many of the developing countries, including the Islamic republic of Iran. Thus, hyperventilation is still the cornstone of treatment of PPHN.

Previous studies have clearly shown that acute hyperventilation can improve PaO2 in neonate with PPHN.[26] Experimental studies suggest that response to alkalosis is transient, and that alkalosis may paradoxically worsen pulmonary vascular tone, reactivity and permeability edema.[27-29] In addition, prolonged hyperventilation reduces cerebral blood flow and oxygen delivery to the brain, potentially worsening neurodevelopment outcome. Mechanical ventilation usingin appropriate setting can produce acute paranchymal lung injury (ventilator induced lung injury; VILI), causing pulmonary edema, decreasing lung compliance and promoting lung inflammation due to increased cytokine production and lung neutrophil accumulation.[30]

Magnesium sulphate has been used since many decades to treat toxemia of pregnancy. Magnesium the natural calcium blocker antagonizes calcium Ion entry into smooth muscle cells, thus promoting vasodilation. It may also exert its favorable influence on nitric oxide synthetase, cyclic nucleotides, endothelins and prostaglandins.[31] Magnesium sulphate has been used successfully in the treatment of PPHN.[32-35] In all the previous studies, magnesium sulphate was tried in newborns with PPHN who did not respond to conventional ventilation. In our study, all the patients who did not respond to conventional ventilation were first treated with mechanical hyperventilation for two hours. None of them responded to hyperventilation but all the patients showed improvement in oxygen saturation after magnesium sulphate administration and 9 out of 10 patients survived. The neurodevelopment assessment of infants who survived was normal at six months age. We conclude that magnesium sulphate is a non-aggressive and low cost treatment of short duration which is easy to apply. This report provides evidence that magnesium has a role in the treatment of PPHN patients who do not respond to hyperventilation or may be applied instead of hyperventilation.

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