The Role Of Magnesium Sulfate In The Treatment Of Persistent Pulmonary Hypertension In The Neonate: Our Experience In King Hussein Medical Centre (KHMC).

Alaeddin Ali Saleh MD,Abdalrazzaq Ahmad Alyassen MD, Aghadir Mohammad Alhadidi MD
Fadi Farhan Ayash MD

ABSTRACT

Persistent pulmonary hypertension in neonates (PPHN) is a critical condition caused by a failure in normal cardiac-pulmonary adjustment after birth; many factors can interfere with this process, such as meconium aspiration, Parenchyma lung disease, sepsis, intrauterine and/or prenatal hypoxia, and abnormal pulmonary development.

Objectives: This study was conducted to evaluate the effect of magnesium sulfate ($MgSO_4$) as a treatment for persistent pulmonary hypertension of the newborn (PPHN) and its outcome.

The treatment of persistent acute pulmonary hypertension of newborn remains controversial and has been tried in various treatment modalities. This study was conducted to evaluate the effect of magnesium sulfate ($MgSO_4$) as a treatment for persistent pulmonary hypertension of the newborn (PPHN) and its outcome.

Methods and Statistics: This study is a retrospective review of a neonate with PPHN treated with magnesium sulfate ($MgSO_4$) at King Hussein Medical Centre (KHMC) neonatal intensive care units during the period of January to December of 2018. Our sample covers nineteen newborn babies admitted to the neonatal intensive care units (NICU) out of 10155 deliveries, with respiratory failure and profound hypoxemia resulting from persistent pulmonary hypertension, were enrolled in the study.

All patients underwent the following tests: full blood count, kidney function test, arterial blood gas, blood culture, chest x-ray, and echocardiograms. All patients with congenital heart disease excluded from this study.

Statistics and data described in terms of median, mean ± standard deviation (± SD) frequencies and percentages. Statistical calculations were carried out using Microsoft Excel 2010 computer programs and the Statistical Package for the Social Sciences (SPSS) version 18.

Results: The total number of 19 cases of PPHN from 10155 deliveries, by year, admitted to neonatal units at KHMC during 2018. Male newborns with PPHN were 10 (53%), while the female newborns were 9 (47%). The number of newborns with lung hypoplasia was 4 (21%), prematurity was 7 (37%), respiratory distress syndrome (RDS) was 12 (63%), sepsis was 9 (47%), congenital diaphragmatic hernia was 2 (10%), birth asphyxia was 2 (10%). Sildenafil used in 4 (23 %) cases treated with magnesium sulfate. The number of deaths was 7 (37%).

Conclusion: This study provides evidence that magnesium sulfate can play a part in the therapy of PPHN. It is a non-aggressive treatment of short-duration and low cost.

Keywords: Persistent pulmonary hypertension in the newborn (PPHN), magnesium sulfate, Sildenafil, pulmonary arterial pressure (PAP).

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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is described as a persistence of the fetal circulatory pattern of right-to-left shunting across the patent's ducts arteriosus and patent foramen oval as a result of excessive pulmonary artery resistance([1]). This, in turn, leads to extreme hypoxemia that might not respond to standard respiratory support.

From the departments of pediatrics medicine.
Correspondence should be addressed to Dr. Alaeddin Ali Saleh MD,E-mail:alaeddin_alali@yahoo.com.
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There are many factors and causes that lead to newborns with high pulmonary artery pressure, including a primary cause (very rare) or secondary to severe lung disease (e.g. meconium aspiration syndrome, surfactant

deficiency) infection (e.g. pneumonia), perinatal asphyxia, structural abnormalities (e.g. congenital heart disease, congenital diaphragmatic hernia) ([2]). The incidence is 1/500-1,500 live births, with a wide variation among clinical centers, with an estimated mortality of 10-20% ([3]) and approximately 25% of survivors of neonatal display significant neurodevelopmental impairment when tested at 12 to 24 months of age ([4]).

The initial finding of PPHN is respiratory distress and cyanosis, and this may occur despite adequate ventilation, in addition to tachypnoea, retraction and may have a significant decrease in pulse oximetry reading with routine nursing care or minor stress.

Other clinical findings are highly variable depending on the severity, stage and other associated disorders (particularly pulmonary and cardiac disease) ([5]).

The diagnostic criteria of PPHN include ([6]): (1) severe hypoxia (PaO_2<50 mm Hg in 100% inspired oxygen and appropriate ventilation).

(2) supra systemic pulmonary blood pressure (can be estimated by echocardiography). (3) Normal cardiac anatomy: cyanotic congenital heart defect should be excluded by echocardiography. (4) Evidence of right-to-left shunting: bidirectional flow across a patent ductus arteriosus or foramen oval on echocardiography.

The treatment approach for PPHN is still controversial, and various modalities of treatment have been tried, including; supplemental oxygen, intubation, mechanical ventilation, nitric oxide, sedation and analgesia, pharmacological agents (dopamine, epinephrine, Sildenafil, magnesium sulfate) and extracorporeal membrane oxygenation (ECMO) ([7]).

Neonates who develop PPHN are at approximately 20% risk of rehospitalization within one year of discharge and have a 20% to 46% risk of audiology, neurodevelopmental, or cognitive impairments ([8]).

Methods

This study is a retrospective review of a neonate with PPHN treated with magnesium sulfate ($MgSO_4$) in the neonatal intensive care units at KHMC during the period of January to December of 2018.

The diagnosis of PPHN was considered when there was persistent hypoxemia (PaO_2 of <50 mm Hg or 6.67 kPa) not proportionate to the degree of severity on the chest radiograph, despite the adequate ventilator support and/or important liability of oxygenation with significant variations in PAO2 without changes in ventilator settings.

Congenital cyanotic heart disease excluded and pulmonary hypertension always confirmed by echocardiography ([9]) through measurement of their estimated pulmonary arterial pressure (EPAP). Neonates with EPAP more than 50 mm Hg included.

Mean Apgar scores were seven at one minute and nine at five minutes. Gestational age, type of delivery, birth weight, primary diagnosis, ventilator settings, arterial blood gas, magnesium, calcium, electrolytes, and vital signs were measured. All patients were first given routine supportive treatment, including (1) hemodynamic support by volume expansion up to 20 to 30 ml/kg and, if necessary, with a continuous dopamine infusion at 2 to 20 mcg/kg/minute; (2) sedation with morphine infusion at 10 to 20 mg/kg/hour and; (3) appropriate ventilatory support (Nasal continuous positive airway pressure (NCPAP), Synchronized Intermittent-Mandatory Ventilation (SIMV), High frequency oscillatory ventilation (HFOV).

Before $MgSO_4$ infusion was begun, all infants were ventilated with 100% FiO_2 at a rate of 45 breaths/minute with high peak inspiratory pressure (PIP) of 25 cm H_2O and positive end-expiratory pressure (PEEP) of 3-5 cm H_2O ([10]). A loading dose of 200 mg/kg $MgSO_4$ diluted to 8-10% in sterile water was given intravenously over 30 minutes, followed by a continuous infusion of 20 to 50 mg/kg/hour, to obtain a magnesium blood concentration between 1.5-2.5 mg/dl. Magnesium blood concentrations were monitored before and every 6 hours after we gave magnesium sulfate, within the first 24 hours, and every 12 hours after stabilization. Before and during $MgSO_4$ treatment, heart rate, mean arterial blood pressure (MAP), temperature, and ventilator settings with inspired oxygen fraction (FIO_2), respiratory rate, peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and mean airway pressure (MAP) recorded at two-hour intervals, during the first day of treatment, and then four to six times a day.

We depend on three indicators for the treatment responder (1) pulmonary arterial pressure (PAP). (2) Continuous pulse oximetry recorded serial rise to≥90%. (3) Repeated arterial blood gas measurement recorded at PaO_2> 60 mm Hg.

Result

The total number of 19 cases of PPHN from 10155 deliveries, by year, admitted to neonatal units at KHMC during 2018.

Table 1 shows the descriptive study data, such as gender distribution, gestational ages, and delivery modes.

Male newborns with PPHN were 10 (52.63%), while the female newborns were 9 (47.37%). Full-term cases

(>37weeks) were 9 (47.37%), the number of 30-37 weeks was 4 (21.05%), and the number of less than 30weeks was 6 (31.58%). The normal delivery number was 7 (36.84%) while the cesarean section number was 12 (63.16%). Babies with a birth weight higher than 2.4 kg were 8 (42.10%), while babies with a birth weight less than 2.4 kg were 11 (57.89%).

Table I: Summary of sex distribution, gestational ages and delivery modes of neonates with PPHN

	Number	Percentage
Sex		
Male	10	52.6
Female	9	47.4
Gestational Age (weeks)		
FT (37 weeks)		
30-37 weeks	9	47.4
Less than 30 weeks	4	21.1
	6	31.5
Mode of Delivery		
Normal delivery	7	36.8
Cesarean section	12	63.2
Birth Weight		
Higher than 2.4 kg	8	42.1
Less than 2.4 kg	11	57.9

Regarding PPHN clinical diagnosis, this study candidate presented with lung hypoplasia, prematurity, respiratory distress syndrome (RDS), sepsis, congenital diaphragmatic hernia and birth asphyxia (Table II).

Table II: Clinical diagnosis of neonates with PPHN.

	Number	Percentage
Lung hypoplasia	4	21.1
Prematurity	7	36.8
RDS	12	63.2
Sepsis	9	47.4
congenital Diaphragmatic hernia	2	10.5
Birth asphyxia	2	10.5

The number of newborns with lung hypoplasia was 4 (21.05%), prematurity was 7 (36.84%), RDS was 12 (63.16%), sepsis was 9 (47.36%), the congenital diaphragmatic hernia was 2 (10.53%), and birth asphyxia was 2 (10.53%).
Hypotension is the only side effect registered in our cases with a total numer of 8 and a percentage of (42.11%) of the cases using magnesium sulfate. Sildenafil used in 4 (21.05%) cases treated with magnesium sulfate. The number of deaths was 7 (36.84%).

Primary outcome measure

Neonates showed a significant drop of pulmonary artery pressure (PAP) at 48 hours and five days after initiation of magnesium sulfate therapy, compared to baseline PAP. Significantly lower in PAP (P3) of 23.7 ± 3.7 mm Hg five days after therapy (Table III).

Table III: Estimated Pulmonary Artery Pressure (EPAP) in the Study candidates.

	Mean	Standard deviation
EPAP before treatment mm Hg	57.1	± 8.6
EPAP (48 hours after treatment) mm Hg	43.8	± 11.5
EPAP (after five days of treatment) mm Hg	37.2	± 3.6

Secondary outcome measures

An essential factor indicating an improvement of the patient is the time interval to normalization of oxygen saturation (SaO_2) and arterial blood gases (ABG). Neonates treated with magnesium sulfate therapy showed a significantly shorter interval to oxygen saturation normalization, arterial blood gases, and duration of ventilation (Table IV).

Table IV: Duration of SaO_2 Improvement, ABG and Duration of Ventilation by Days.

	Median	Std. deviation
Time interval to SaO_2 normalization (days)	1.4	-
Time interval to ABG normalization(days)	1.60	± 0.4
Duration of ventilation (days)	5.5	± 2.44

Mortalities

Seven (36.84%) babies died (figure 1), 2 showed congenital diaphragmatic hernia, and 5 showed sepsis.

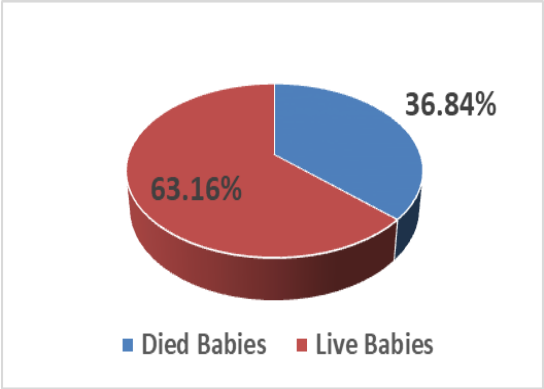

Figure 1: Mortality Rate in PPHN After We Used Magnesium Sulfate**.**

Discussion

PPHN is an important neonatal emergency contributing to neonatal hypoxia, which is often associated with high mortality. Most types of PPHN treatments, including nitric oxide and ECMO, are effective but not available in our country. Hence the search for other options is crucial this study aimed at assessing the role of magnesium sulfate in the treatment of PPHN in neonates and concluded that magnesium sulfate is effective and relatively safe compared to outcome rates of adverse effects.

There is limited information on the use of $MgSO_4$ to treat PPHN. Several clinical studies reviewed. Some of these studies performed on infants in the full term. All of these studies used a comparable dose plan, with a

loading dose of 200 mg/kg over 20-30 minutes, followed by continuous infusion of 20 - 150 mg/kg/hour, given for up 5 days ([11-13]).

The serum magnesium level measured in the present study; however, blood pressure and the response to hypotension were monitored, $MgSO_4$ infusion discontinued temporarily, and the saline infusion was given. Hypotension observed in 8 (42.1%) neonates; this percentage was higher than the result reported by Daffa and Milaat [11]. Abu-Osba observed transient bradycardia [15], which is not seen in the present study. Flaccidity was seen in one of the study candidates. However, other side effects of $MgSO_4$ (hypocalcemia and GIT disturbance) not found in the present work, which is in agreement with other studies ([11,14-16]).
In this study, patients not monitored for negative neurological effects, but previous studies have found that patients have a normal neurological examination in one year [11, 14].

The primary outcome measure reported a drop in EPAP by echocardiographic evaluation. Not all other studies followed up with echocardiography of patients. Abu-Osba [15] reported a comparable rate of improvement.

Secondary outcome measure showed oxygenation improvement by changes in partial oxygenation pressure and ventilatory requirements, where significant improvement of patients' oxygenation parameters was observed at 48 hours, which is in line with previous studies [13-14].

Seven (36.8%) neonates died, while 12 (63.2%) survived, after treatment with magnesium sulfate. Abu-Osba reported [15] that the survival rate was 7 out of 9. Daffa [11] recorded a survival rate of 7 out of 8. However, Tolsa et al. [16] and Chandran et al. [14] all included studies patients have survived. Seven of the study patients, who died, suffered sepsis (5 patients), 2 (congenital diaphragmatic hernia) and this cannot be considered therapy failure because congenital diaphragmatic hernia has remained the most challenging condition to treat successfully despite all the advances in neonatal critical care ([17]).

Conclusions

The study concluded that magnesium sulfate ($MgSO_4$) could be used as a safe and effective method of treating PPHN. It may have a place in the treatment of PPHN, especially in areas where NO and ECMO are not available.
The $MgSO_4$ treatment showed good results with regard to survival rates and side effects. PAP was significantly reduced after five days of therapy in neonates receiving $MgSO_4$.

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