Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v29i03.4677

MAGNESIUM SULPHATE VERSUS SILDENAFIL IN TREATMENT OF PERSISTENT PULMONARY HYPERTENSION IN NEWBORNS

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Abstract:
Objective: To compare the efficacy of Magnesium Sulphate and Sildenafil in treating PPHN in newborn.

Methods: A randomized controlled study evaluated sildenafil with magnesium sulfate in 50 newborns with PPHTN. This study was done at Al-Azhar University hospitals NICU. Study subjects were split into two groups: Sildenafil-treated 25 neonates are Group 1. Group 2: 25 magnesium sulphate-treated newborns. To assess PPHN severity, an expert pediatric cardiologist monitored patients regularly. PPHN treatment entails reducing pulmonary vascular resistance below 20 mmHg and elevating systemic blood pressure to shift blood flow from the right-to-left shunt. Above 95% arterial oxygen saturation and below 30 mmHg tricuspid valve insufficiency. **Results:** EF was similar in both groups. Group 1's PASP by TR peak velocity dropped significantly during 3 days. Group 1's PASP by PI peak velocity dropped significantly over 3 days. Group 2's PASP by PI peak velocity dropped significantly over 6 days. Baseline PASP was similar between groups. Group 1's PASP dropped significantly after 14 days. A significant difference in SaO2 and ABG improvement time and ventilation days between groups.

Conclusion: This study shows magnesium sulfate and oral sildenafil can treat neonatal critical care unit PPHN without inhaled nitric oxide. Both medications have equal side effects and survival. Sildenafil reduced airflow. More research is needed to confirm and assess both drugs' long-term

dangers. Oral sildenafil or intravenous MgSO4 are recommended when other therapies fail. Research is needed to help PPHN newborns. These medications' dose effects need more research.

Introduction

Defined standards for detecting Pulmonary hypertension (PH) is characterized by a mean pulmonary artery pressure of 20 mm Hg or above at rest, as determined by right heart catheterization(1).

Persistent pulmonary hypertension of the neonate (PPHN) is defined by severe hypoxemia, elevated pulmonary vascular resistance, and the presence of right-to-left shunting at the atrial and ductal levels. PPHN is a complex and serious sickness that is difficult to treat. PPHN is predicted to occur in 2 to 6.8 instances per 1,000 live births, with a death rate ranging from 10% to 20%(2).

Iloprost, sildenafil, and inhaled nitric oxide (iNO) are used to treat pediatric patients with pulmonary arterial hypertension (PAH). Sildenafil is a primary medication used in this scenario and has greatly improved the survival rates of children with severe PPHN, increasing from less than one year for untreated children in the 1980s to 97% over five years. Recent FDA advise has caused pediatricians to be cautious about prescribing sildenafil to minors with PAH. This correspondence aims to analyze the role of sildenafil in treating pediatric PPHN(3).

Magnesium sulfate functions as a natural calcium channel blocker by inhibiting the influx of calcium ions into smooth muscle cells, leading to vasodilation. Magnesium sulfate is a cost-effective and safe option for the initial management of moderate PPHN. It is utilized as an alternate therapy for PPHN when traditional medications are ineffective, discouraged, or not accessible(4).

This study aims to evaluate the efficacy of sildenafil and magnesium sulfate in neonates with PPHN.

Methodology

Study design

A randomized controlled clinical trial was carried out on 50 neonates with PPHN to examine the effectiveness of sildenafil and magnesium sulfate.

Study setting

This study was conducted at Al-Azhar University hospitals NICU

The studied subjects were classified into 2 groups:

Group (1): include 25 neonates who received sildenafil.

Group (2): include 25 neonates who received Magnesium Sulphate.

Time of administration of treatment

14 days during which full-term neonates younger than 10 days at birth are considered.

Inclusion criteria:

Full-term newborns under 10 days old with persistent pulmonary hypertension, (PaO_2 < 50 mm Hg), and PASP by TR peak velocity above 40 mm Hg.

Exclusion criteria:

The study excluded preterm neonates under 37 weeks gestation, full-term neonates with congenital cardiac disease, Lung anomlies or hypoplasia, predisposition for bleeding, and liver dysfunction.

Methods

The study was carried out in 4 phases:

1. First phase: Enrollment and selection phase.
2. Second phase: Intervention phase and monitoring.
3. Third phase: Evaluation phase.
4. Fourth phase: collected data analysis and results.

First phase: (Enrollment and selection phase):
All newborn in our trial were subjected to the following:
➢ Consent was obtained from parents for the intervention. The medical ethics committee approved the study.
➢ Obtain a thorough pregnancy and perinatal history, including any maternal illnesses or obstetric issues that could affect the newborn, as well as the use of antenatal steroids.
➢ Full resuscitation data according to Neonatal resuscitation program (NRP).
➢ Gestational age (GA), birth weight (BW), and sex.
➢ Full physical and neurological assessment.
➢ Thorough history taking: (Age, sex, weight)
➢ PH history
➢ Complete clinical examination
➢ Oxygen saturation (SPo_2), oxygenation index (OI) is calculated
➢ An echocardiography was conducted before to enrollment to detect a right-to-left shunt, assess pulmonary artery pressure, and confirm the absence of cyanotic heart disease.

➢ **Radiological investigation:**
- HRCT chest
- Chest X rays

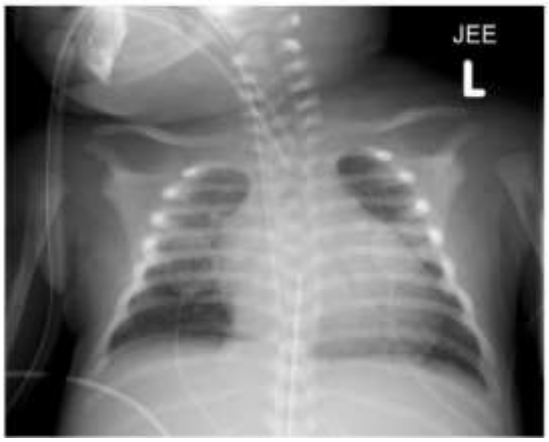

Figure (1): CXR of newborn

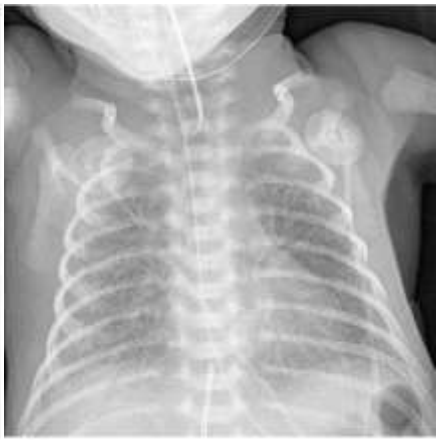
Figure (2): CXR of newborn

Second phase: Intervention phase and monitoring.
1- Intervention
Time of administration: First 6days of life of full-term neonates.

Dose:
Dose in adults
Sildenafil is given at a dose of 136 mg/kg twice day, while MgSO4 is supplied with a loading dose of 200 mg/kg over 30 minutes, followed by a maintenance dose ranging from 1360 to 3400 mg/kg/hr. Complications of magnesium sulphate may involve hypotension, central nervous system depression, urinary retention, gastrointestinal disturbance, and disturbances in calcium and potassium levels.

Dose in neonate
Clark's rule is a technique utilised to determine the appropriate pharmacological dosage for paediatric patients by considering their weight and the standard adult dose of the medication. Clark's rule equation is the patient's weight in pounds divided by 150 pounds (68 kg) multiplied by the adult drug dose to determine the paediatric medicine dose:

- **(Weight*** divided by 68 kg) x Adult Dose** = Pediatric Dosage**

** The adult dose is the recommended amount of medication for adult use.

***Weight of pediatric patient in kg

Clark's rule is a pediatric medicine dosing guideline in medical literature that uses the patient's weight to determine drug dosage(21).

Administer sildenafil orally at a dose of 0.5-2 mg/kg every 6 hours, with a maximum of 3 mg/kg every 6 hours. Initiate treatment with a lower dosage and frequency, particularly when used in conjunction with other vasodilators. Administer 200 mg (2 ml = 1.6 mEq)/kg of MgSO4 intravenously over 20-30 minutes, then follow with 20-75 mg (0.2-0.75 mL = 0.16-0.6 mEq)/kg/hour. IVI will regulate plasma magnesium levels within the range of 8.5-13.4 mg/dl (3.5-5.5 mmol/L) for a maximum of 5 days.

Group 1 participants were administered sildenafil at a dosage of 2 mg/kg twice daily.

Group 2 got MgSO4 at

• Initial dose: 0.8 mmol/kg

• Maintenance dose should be started following the loading dose.

o The recommended maintenance dose is between 0.08 and 0.3 mmol/kg/hour. o If there is a positive response to the initial dose, the maintenance dose can be continued for up to 5 days.

Duration of therapy

For 14 days during their hospital stay.

2- Monitoring

All participants in the study underwent a follow-up assessment throughout this period. Temperature was recorded every 8 hours.

- Heart rate was measured continuously using cardio-respiratory monitor.
- Mean blood pressure and respiratory rate were recorded every 6 hours, provided that the baby is clinically stable.
- Oxygen saturation (SPo_2) was continuously monitored and kept between 92-95% as possible, using pulse oximeter.
- Echo investigation was repeated after 3 days and 6 days and findings were recorded

Third phase: Evaluation phase:

Patients were consistently monitored at specific time intervals determined by a specialist pediatric cardiologist to assess the severity of PPHN. The treatment objectives for PPHN involve decreasing pulmonary vascular resistance to reach pulmonary pressures below 25 mmHg and elevating systemic blood pressure above pulmonary pressures to redirect blood flow from the right-to-left shunt. Additionally, strive to raise the arterial oxygen saturation level > 95% and limit the severity of tricuspid valve insufficiency to less than 30 mmHg (4).

The reduction in Pulmonary Artery Systolic Pressure, as determined by echocardiography, from the baseline measurement to the fourteenth day after medicine was given and was used to evaluate efficacy. Safety assessment was conducted by tracking adverse events associated with the medication. Active surveillance was employed to evaluate patients daily for ADRs (hypotension, gastrointestinal intolerance, bleeding, and pulmonary hemorrhage) while receiving the research therapy.

Fourth phase: Statistical analysis:

Results were analyzed statistically by SPSS program with P value <0.05 as a level of significance and was used to process and analyze the data.

Results

Table (1): Demographic data among our cases.

		Group (1) (n=25)	Group (2) (n=25)	P value
Age (days)		3.24 ±1.2	3.22 ±1.21	0.96
Sex	**Male**	12 (48%)	13 (52%)	0.77
	Female	13 (52%)	12 (48%)	
Duration of hospital stay (days)		7.29 ± 1.1	8.3±2.5	**<0.001**

Chi Square, t Test, p value >0.05: nonsignificant, p value <0.05 significant

Group 1 had an average age of 3.24 days and a standard deviation of 1.2. There were 12 instances of males in the group. The mean length of hospitalisation was 7.29 ± 1.1 days. In group 2, the mean age was 3.22 days with a standard deviation of 1.21. There were 13 male instances. The mean length of hospitalisation was 8.3±2.5 days. There were no notable discrepancies in demographic characteristics between the two groups. There was a significant disparity in the length of hospitalisation between the two groups.

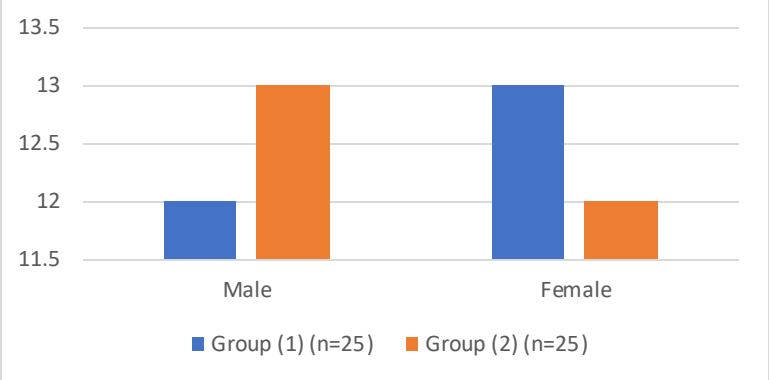

Figure (3): Sex.

Table (2): Gestational age and mode of delivery among our cases.

		Group (1) (n=25)	Group (2) (n=25)	P value
Gestational age in weeks (mean ± SD)		38.4 ± 0.4	38.82 ± 0.45	0.56
Mode of delivery	Cesarean section	18 (72%)	17 (68%)	0.75
	Vaginal delivery	7 (28%)	8 (32%)	

Chi Square, T t Test, p value >0.05: nonsignificant, p value <0.05 significant

In group 1, the average gestational age was 38.4 ± 0.4. There were 18 Cesarean sections performed. Group 2 had a mean gestational age of 38.82 ± 0.45, with 17 instances undergoing Cesarean section. There were no significant differences between the two groups in terms of gestational age and manner of birth.

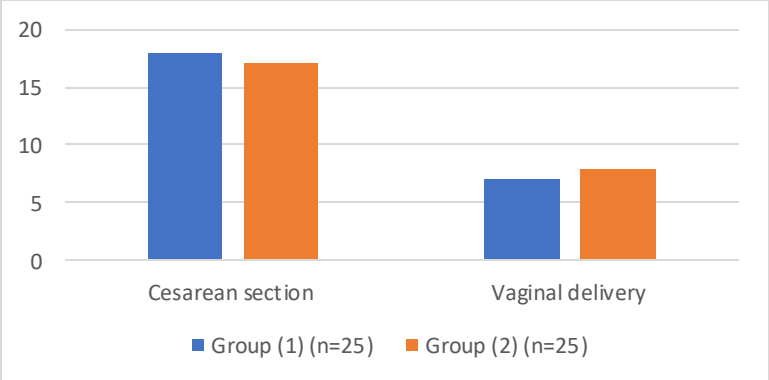

Figure (4): Mode of delivery.

Table (3): APGAR score and Birth weight.

	Group (1) (n=25)	Group (2) (n=25)	P value
APGAR score at five minutes (mean ± SD)	8.39 ± 0.33	8.45 ± 0.35	0.76
Birth weight in grams (mean ± SD)	2189 ± 174	2201 ± 172	0.9

T t Test, p value >0.05: nonsignificant, p value <0.05 significant

In group 1, the average APGAR score at five minutes was 8.39 ± 0.33, as seen in the table. The birth weight was 2189 grams with a standard deviation of 174. The average APGAR score at five minutes in group 2 was 8.45 ± 0.35. The birth weight was 2201 grams with a standard deviation of 172. There were no notable disparities in APGAR score and birth weight between the two groups.

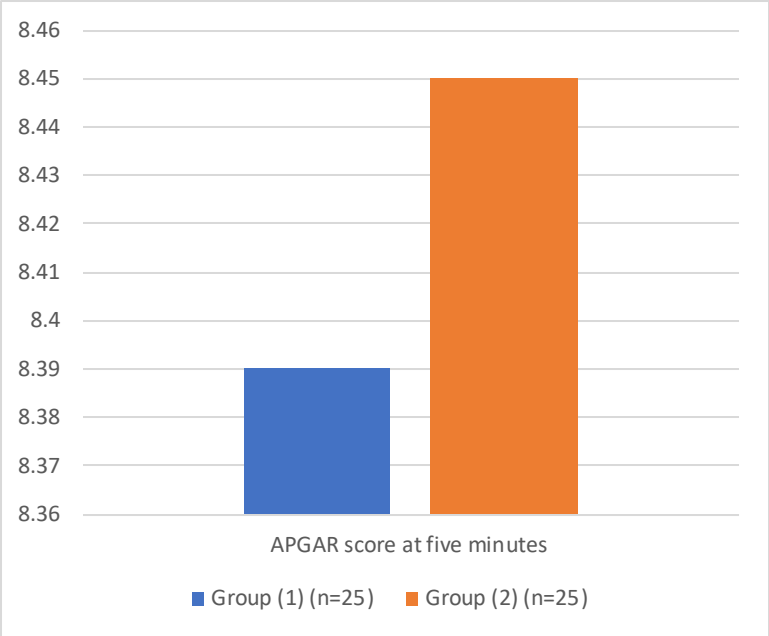

Figure (5): APGAR score.

Table (4): ECHO among our cases.

Mean PASP from peak PR velocity	**Group (1) (n=25)**	**Group (2) (n=25)**	P value
Baseline (mmHg)	26.7 ± 7.45	24.13 ± 7.12	0.82
3 days	15.72 ± 3.5	16.45 ± 5.4	**0.03**
6 days	8.41± 2.34	16.44 ± 4.2	**0.005**
PASP by TR peak velocity			
Baseline	63.6 ± 6.2	64.7 ± 6.22	0.91
3 days	42.5 ± 8.24	50.34 ± 5.1	**0.022**
6 days	37.1 ± 6.2	41.22 ± 9.2	0.058
EF %			
Baseline	62.7 ± 6.8	62.3 ± 6.1	0.59
3 days	63.1 ± 5.5	63.3 ± 5.2	0.78
6 days	66.2 ± 4.4	66.2 ± 4.5	0.913

T t Test, p value >0.05: nonsignificant, p value <0.05 significant, TR=Tricuspid regurgitation, EF=Ejection fraction.

This table indicates that there was no significant difference between both groups in terms of EF. Group 1 experienced a substantial decrease in PASP by TR peak velocity over a period of 3 days. There was a substantial drop in mean PASP from peak PR velociy during a 3-day period in group 1.

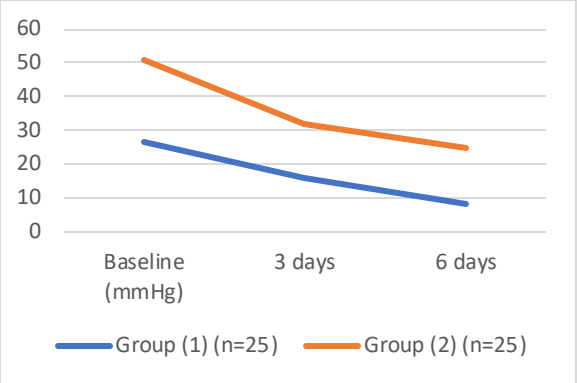

Figure (6): PASP by TR peak velocity.

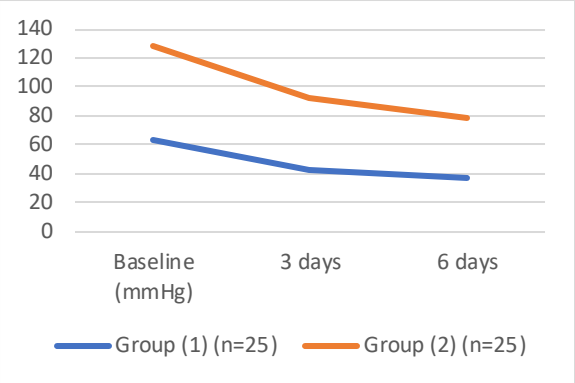

Figure (7): PASP by TR peak velocity.

Table (5): PASP measured by echo

	Group (1) (n=25)	Group (2) (n=25)	P value
PASP			
Baseline	46±11	45±12	0.67
14 days	29±4	34±7	**0.008**

t Test, p value >0.05: nonsignificant, p value <0.05 significant

This table indicates that there was no significant difference between the two groups in terms of Baseline PASP. Group 1 experienced a substantial drop in PASP after 14 days.

Table (6): Outcome data.

	Group (1) (n=25)	Group (2) (n=25)	P value
Duration until SaO2 returns to normal levels (days)	2.2± 0.76	3.62± 1.75	<0.001
Duration until arterial blood gas normalization (days)	2.45± 0.8	3.7± 2.8	<0.001
Duration of ventilation (days)	4.7± 1.14	6.5± 2.45	<0.001

T Test, p value >0.05: nonsignificant, p value <0.05 significant

This table demonstrates a substantial difference between both groups in terms of the time taken for SaO2 and ABG improvement, as well as the duration of ventilation in days.

Table (7): Comparison between both groups as regard radiological investigation

	Group (1) (n=25)	Group (2) (n=25)	P value
Cardiomegaly by chest X-ray	15 (60%)	18 (72%)	0.28

t Test, p value >0.05: nonsignificant, p value <0.05 significant

This table demonstrates a substantial difference between both groups in terms of Cardiomegaly by chest X-ray

Discussion

Despite being acknowledged for over thirty years, the etiology and optimal therapeutic approach for persistent pulmonary hypertension (PPHN) remain unidentified. Research on the causes, risk factors, outcomes, and treatment choices for PPHN(2) is limited.

The syndrome is caused by acute hypoxia, chronic foetal hypoxia, and the pulmonary artery's inability to adapt to rising oxygen levels. Increased smooth muscle thickness in the pulmonary artery may be linked to all three illnesses. Contraction of smooth muscles in the pulmonary arteries can lead to decreased ventilation and lung expansion, resulting in a reduced lumen diameter, increased pulmonary artery resistance, and elevated pulmonary arterial pressure (PAP). This may occur either completely or partially.

A recent review concluded that Sildenafil is the most effective treatment for PPHN, whether given alone or in combination with iNO. Access to inhaled nitric oxide (iNO) or extracorporeal membrane

oxygenation (ECMO) is limited in underdeveloped nations. Neonates at our facility diagnosed with Persistent Pulmonary Hypertension of the Newborn (PPHN) are frequently administered sildenafil therapy in addition to receiving supportive care. Supportive care methods for managing PPHN involve nourishment provision, body temperature maintenance, stress reduction, and gentle handling of the newborn, all of which are essential components.

Phosphodiesterase-5 (PDE5) is more abundantly produced and activated in lung tissue compared to the heart. PDE5 is a potential therapeutic target for conditions affecting pulmonary circulation, such as pulmonary arterial hypertension and lung disorders. Sildenafil is the initial oral medication that enhances NO-related vasodilation in locations with perfusion demand and decreases inefficient lung perfusion (venous admixture) and respiration.

In 1991, Haynes and colleagues found that zaprinast reduced the vasoconstriction reaction of isolated rat lungs to sudden alveolar hypoxia. Intact anesthetized newborn lambs and chronically hypoxic rats both experienced selective dilation of pulmonary arteries when subjected to acute hypoxia. The PDE5 inhibitor E4021 showed greater specificity for pulmonary circulation and did not dilate systemic circulation at the dosage used in the study. Zaprinast inhibited rabbit lung human papillomavirus. Sildenafil inhibited HPV in isolated perfused rodent lungs, demonstrating that PDE5 inhibitors are powerful pulmonary vasodilators. Oral administration of sildenafil reduced pulmonary hypertension in mice exposed to chronic hypoxia.

Zhao and colleagues showed that the PDE5 inhibitor has effects that go beyond NO generated from eNOS. Sildenafil's anti-remodeling effects on the pulmonary vasculature and right ventricle were reduced in NPR-A mutant mice, indicating the involvement of natriuretic peptides that elevate intracellular cGMP levels through the activation of receptor-linked particulate guanylate cyclase. Sebkhi et al. discovered that therapeutic sildenafil reduces pulmonary artery pressure and vascular muscularization in the lungs of rats. This study deviates from previous studies by starting the therapy of rats with chronic hypoxia at the onset of hypoxia.

Research shows that blocking PDE5 is more efficient in decreasing pulmonary hypertension and vascular resistance. The specific pulmonary impacts of PDE5 inhibitors may result from increased amounts of nitric oxide production in the lungs and pulmonary PDE5 compared to the rest of the body, comparable to the corpus cavernosum. Itoh and colleagues performed experimental trials to investigate the efficacy of sildenafil for treating pulmonary arterial hypertension (PAH).

Sustained administration of sildenafil decreased right ventricular systolic pressure, right heart hypertrophy, and medial wall thickness in rats with monocrotaline-induced pulmonary hypertension. Sildenafil successfully treated pulmonary hypertension. In chronically unwell rats, sildenafil decreased the expression of MMP 2 and 9, pulmonary artery pressure, and vascular muscularization in the lungs.

There were fewer fully muscularized small pulmonary arteries. Typically, blood pressure in the pulmonary arteries is significantly lower than in other parts of the body. Before birth, the muscle around the pulmonary arteries is tightly compressed, leading to increased pressure. Following birth, vessels widen and blood pressure decreases. Infants with PPHN do not undergo a decrease in blood pressure due to several factors. Magnesium sulfate widens the muscles of the pulmonary artery.

When administered intravenously, it impacts other muscles and arteries. Even while it may be effective for pulmonary hypertension, it could lead to adverse side effects in other areas of the body. This study aims to assess the effectiveness of sildenafil and $MgSO_4$ in infants with PPHN.

The average age of participants in group 1 was found to be 3.24 ± 1.2 days in our investigation. Twelve cases involved boys. The average length of hospitalisation was 7.29 days, with a standard deviation of 1.1 days. The mean age of the participants in group 2 was 3.22 days, with a standard deviation of 1.21 days. Thirteen cases involved guys. The average length of hospitalisation was 8.3 days with a standard deviation of 2.5 days. There were no significant demographic differences between the two categories. Significant differences existed in the length of hospital stay between the two groups.

There is scarce data available about the utilisation of $MgSO_4$ for PPHN. Five uncontrolled clinical investigations conducted by Chandran et al. and Abu-Osba et al. The Cochrane team found studies

by Tolsa et al., Daffa et al., and Wu et al. that were published in 2007. Four studies were conducted on full-term neonates with a similar gestational age as the study group in Shaltout et al., where the average gestational age was 37.1 ± 1.14 weeks. All studies administered a 200 mg/kg loading dose over 30 minutes, followed by a continuous infusion ranging from 20 to 50 mg/kg/hr.

Our research showed no statistically significant disparities in EF between the two groups. Group 1 experienced notable decreases in pulmonary artery systolic pressure (PASP) as indicated by tricuspid regurgitation peak velocity throughout a 3-day timeframe. Three days later, there was a significant reduction in pulmonary artery systolic pressure by peak velocity in group 1. After six days, there was a significant decrease in pulmonary artery systolic pressure by peak velocity in group 1.

Engelbrecht et al. (2008) detailed the use of Sildenafil in two nonventilated babies with moderate to severe Persistent Pulmonary Hypertension of the Newborn (PPHN) from South Africa. Introducing Sildenafil to the treatment regimen resulted in significant enhancements in haemoglobin oxygen saturation measured by pulse oximetry, cessation of oxygen therapy, and prevention of mechanical ventilation.

Herrera et al. (2006) observed a notable improvement in the Oxygenation Index (OI) in infants with Persistent Pulmonary Hypertension of the Newborn (PPHN) who received Sildenafil compared to those who received a placebo. In addition, the average airway pressure and duration of ventilation decreased, and there was an enhancement in PaO2 levels after 72 hours in the Sildenafil group.

Baquero et al. (2006) undertook a randomised double-blind trial to evaluate the effects of Sildenafil on oxygen levels in infants with Persistent Pulmonary Hypertension of the Newborn (PPHN). The infants had severe Persistent Pulmonary Hypertension of the Newborn (PPHN) with an oxygenation index (OI) of 25 or higher. Researchers gave oral Sildenafil to 7 neonates and a placebo to 6 infants. The group that received sildenafil showed improved survival rates in this trial.

Two appropriate studies from environments with limited resources were included in a 2007 Cochrane meta-analysis led by Shah et al. 37 infants participated in both experiments. The group that received sildenafil demonstrated a significant improvement in oxygen levels. The analysis revealed that there were no statistically significant differences in baseline PASP between the two groups. Group 1 showed a notable reduction in PASP within a 14-day timeframe. Shaltout et al.

In 2012, the main focus was on the reduction of EPAP as shown by echocardiographic assessment, with 88 patients showing improvement. Not all other studies conducted patient follow-ups with echocardiography. There were no significant differences in EPAP values between group S and group M at baseline (P1) and after 48 - 72 hours (P2). Group S had a significantly decreased EPAP (P3) of 24.7 ± 3.8 mmHg five days after treatment compared to group M with 36.2 ± 3.2 mmHg (P = 0.012). Abu-Osba et al. documented a similar rate of enhancement.

This study shows a significant disparity between the two groups for the time required for SaO2 and ABG enhancement, as well as the length of ventilation in days.

Shalt out et al. (2012) shown that the time needed to attain normalisation of oxygen saturation and arterial blood gases is a critical factor in patient recovery. Group S demonstrated faster normalisation of oxygen saturation and arterial blood gases, as well as a shorter duration of breathing compared to group M.

The secondary outcome measure evaluated the improvement of oxygen levels by analysing changes in partial pressure of oxygen and ventilatory requirements. The patient's oxygen levels significantly improved after 48 hours, in line with the research conducted by Chandran et al. and Abu-Osba et al. Tolsa et al. and Daffa et al.

Shaltout et al. (2012) conducted a clinical trial where they administered a sildenafil dose of 1mg/kg every 12 hours, although there is no agreement on the best dosage. Baquero et al. prescribed a dosage of 1 mg/kg every 6 hours, whereas Oliver and Webb used a dose of 0.5 mg/kg every 12 hours. The Cochrane team found two uncontrolled clinical studies, first published in 2007 and then updated in 2011. Research on full-term infants demonstrated enhanced oxygenation through alterations in PaO2 levels and reduced need on mechanical ventilation, corroborating our findings. In 2011, Khorana observed elevated oxygen levels in full-term neonates following the administration of sildenafil. Hypotension was an issue in the study, impacting 20% of the newborns who received sildenafil.

According to Shaltout et al. (2012), a recent randomised clinical trial conducted by Uslu et al. compared 34 neonates treated with MgSO4 with 31 neonates treated with sildenafil. The study demonstrated that sildenafil was more effective in treating PPHN by eliciting a quicker clinical response and reducing the duration of mechanical ventilation. The study by Shaltout et al. (2012) determined that both treatments were safe and efficient in managing PPHN. Both groups showed a notable enhancement in their EPAP.

Conclusion

This study proposes that magnesium sulfate and oral sildenafil could serve as substitute therapies for persistent pulmonary hypertension in neonatal critical care units lacking inhaled nitric oxide. Both medicines exhibited similar results in terms of survival rates and adverse effects. Sildenafil was linked to a notably reduced ventilation duration. Further research is needed to confirm this idea and assess the possible long-term negative impacts of both drugs. This proposes use oral sildenafil or intravenous MgSO4 as an alternate treatment in situations where other options are unavailable. Additional research is required to enhance the prognosis for neonates with PPHN. Further research is needed to assess the effects of combining these drugs at different doses.

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