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Comparison between the Efficacy of Either Sildenafil or Magnesium Sulfate Alone Versus Combination of Them in Treatment of Pulmonary Hypertension in Newborns

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ABSTRACT

Background: Pulmonary hypertension of the neonates (PHN) is a syndrome that is distinguished by severe hypoxemia, right-to-left shunt, & elevated pulmonary vascular resistance, all of which are absent indicators of congenital heart disorders.

Objective: This research aimed to compare between either of Sildenafil or magnesium sulfate alone versus combination of both as treatment for pulmonary hypertension in newborns.

Patients and methods: This prospective case-control research was performed on 100 patients (newborns) who had pulmonary hypertension. They were admitted to Neonatal Intensive Care Unit (NICU) at EL Kharga specialized hospital at El Wadi El Gadid. Our cases were separated into three groups: Group A included 30 newborns who were treated with sildenafil, group B contained 30 newborns who were treated with magnesium sulfate and group C that comprised 40 newborns who were treated with both sildenafil plus magnesium sulfate.

Results: There wasn't significant variance among the studied groups regarding echo parameters in all parameters ($P > 0.05$). There was a significant decrease regarding expiratory positive airway pressure (EPAP) in all groups. However, the reduction was better among group C compared to groups A & B ($P < 0.001$). Hypotension incidence was significantly lower among group C compared to the other groups ($P=0.024$).

Conclusion: Magnesium sulfate and sildenafil are safe pulmonary vasodilators for persistent pulmonary hypertension (PPHN) treatment, serving as rescue therapy. Combining these drugs improved the recovery of newborns with PPHN, surpassing monotherapy with only $MgSO_4$ or sildenafil.

Keywords: Magnesium sulfate, Sildenafil, PHN.

INTRODUCTION

Pulmonary hypertension of the newborns (PHN) is a syndrome distinguished by an elevated resistance in the pulmonary vascular of the lungs, a shunt of blood from the right side of the heart to the left side, and severe deficiency of oxygen in the blood, all without any signs of congenital cardiac disorders [1].

The primary objective of pulmonary hypertension of the newborns therapy is to achieve selective pulmonary vasodilation. Several approaches for treating PHN involve ventilation strategies such as high-frequency oscillatory ventilation (HFOV), pulmonary vasodilators including sildenafil, magnesium, adenosine, bosentan, prostacyclin, & tolazoline, as well as specialized medicines such as inhaled nitric oxide (iNO) [2].

Magnesium sulfate ($MgSO_4$) is an element that occurs naturally that blocks calcium channels, preventing calcium ions from entering smooth muscle cells. This action promotes the widening of blood vessels (vasodilation) [1]. Magnesium sulfate is a cost-effective and secure option for initial treatment in cases of moderate pulmonary hypertension of the newborns. It is selected as an alternate treatment for PHN when other conventional medications prove ineffective, are contraindicated, or are unavailable [3].

Sildenafil is a strong & specific inhibitor of cGMP-specific phosphodiesterase 5 (PDE5). This isoenzyme catalyzes the metabolism of cGMP, which serves as the second messenger of NO and plays a key role in relaxing smooth muscle and promoting vasodilation. Sildenafil extends the duration of cGMP's activity by preventing its hydrolytic degradation [4]. The combined administration of sildenafil & $MgSO_4$ has a notable therapeutic impact on persistent pulmonary hypertension of the newborn. This effect can be related to a decrease in the levels of inflammatory markers [5, 6].

The goal of the present research was to compare & evaluate the efficacy of Sildenafil and magnesium sulfate, both individually and in combination, as potential treatments for pulmonary hypertension in infants.

PATIENTS AND METHODS

This prospective case-control research was performed on one hundred cases (newborns) who had pulmonary hypertension and were admitted to NICU at EL Kharga specialized hospital at El Wadi El Gadid. Our cases were separated into 3 groups: Group A that included 30 newborns who were treated with sildenafil, group B contained 30 newborns who were treated with magnesium sulfate, and group C that comprised 40 newborns who were treated with both sildenafil plus magnesium sulfate.

Inclusion criteria: Term & near term (35–42 gestational week) neonates. Both males and females were included. Hypoxemic respiratory failure associated with PHN.

Exclusion criteria: Respiratory distress syndrome (RDS), Neonates with congenital cyanotic heart disease (CCHD) & hypoxic ischemic encephalopathy (HIE).

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All patients were exposed to:

Complete history taking from parents: Personal history (name, age, gestational & labor history and family history (Illnesses - hypertension, cardiac disease, diabetes, stroke, abnormal bleeding, cancer, allergy & asthma), mental retardation, epilepsy, chromosomal problems, congenital anomalies, consanguinity and growth problems.

Physical examinations: General examination including vital signs (Temperature, blood pressure, respiratory rate & heart rate), cyanosis, pallor, lymph node enlargement, & jaundice)).

Investigational studies:

Routine laboratory investigations: CBC [red blood cells (RBCs), hemoglobin concentration (Hb%), platelet count, erythrocyte sedimentation rate, white blood cells (WBCs), and C-reactive protein]**.** Renal function tests (serum creatinine, urine analysis & blood urea). Liver test profile [Serum aspartate, serum albumin, alanine aminotransferases (ALT and AST), serum bilirubin, prothrombin time, serum gamma-glutamyl transferase (GGT) & international normalized ratio (INR)].

Radiological investigation:

Echocardiography (Portable equipment and probes with a frequency range of five to seven megahertz)**:** Observation of tricuspid or mitral insufficiency. Assessment of pulmonary artery pressure. Exclusion of other anatomical factors contributing to heart illness.

Electrocardiogram (ECG): There wasn't ECG feature that was specifically designed for PPHN. The ECG may exhibit a right ventricular dominance pattern that is within the typical range for the age.

Group A (S) received oral sildenafil at a dosage of one milligram per kilogram per six hours using a nasogastric tube. The sildenafil solution was made by pulverizing a fifty milligrams tablet of sildenafil in distilled water to attain a concentration of two milligrams per milliliter. The adverse effects of sildenafil were monitored in relation to the occurrence of hypotension, blood loss propensity, rash, & diarrhea. Group B (M) received $MgSO_4$ loading dosage of two hundred milligrams per kilogram, which was administered over a period of thirty minutes. This was followed by a maintenance dose of twenty to fifty milligram per kilogram per hour. The monitoring of complications of $MgSO_4$ included the assessment of hypotension, urine retention, gastrointestinal disturbance, as well as disturbances in calcium and potassium levels. Group C (S + M) received a combination treatment of sildenafil & magnesium sulfate. Baseline assessment was conducted prior to the initiation of therapy (P1), followed by a measurement taken 48-72 hours later (P2), & another measurement taken five days following the commencement of medication (P3). An estimation of the pressure in the pulmonary artery was obtained by monitoring the peak velocity of the tricuspid regurge. When the velocity of tricuspid regurge was determined utilizing Doppler ultrasound, it was converted into a pressure drop by applying the modified Bernoulli' equation, which is $P = 4\sigma 2$. In this equation, P represents the pressure drop in mmHg, and σ is the velocity of blood in meters per second. The method for evaluating the reduction in pressure from the RV to the RA throughout systole is as follows: The variance between the right ventricular pressure & the right atrial pressure is equal to four times the square of the tricuspid regurge jet velocity.

Ethical consideration: The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant or their parents in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Statistical analysis was performed using SPSS (22.0) for Windows once all data were gathered and processed. A normal distribution of the data was checked using the Shapiro Walk test. The frequency and relative percentages of the qualitative data were presented. We computed the difference between the qualitative variables using the X^2-test and Fisher exact. Mean ± SD was employed to represent parametric data, whereas median and range were used to express non-parametric data. Using normally distributed variables, the one-way ANOVA test was utilized to compare more than two dependent groups. Calculating the difference between parametric and non-parametric quantitative variables in three groups was done using the independent t test and the Mann Whitney test, respectively. P-values less than or equal to 0.05 were considered significant.

RESULTS

Table (1) demonstrated that there wasn't significant distinction between all groups of study according age and sex ($P > 0.05$).

Table (1): Demographic data distribution between the all groups of study

		Group A (S) (N=30)	Group B (M) (N=30)	Group C (N=40)	F / χ^2	P
Age (days) Mean ± standard deviation		4.73 ± 2.68	6.17 ± 4.04	4.63 ± 2.16	2.66	.075
Sex	Male	14 (46.7%)	14 (46.7%)	20 (50%)	.107	.948
	Female	16 (53.3%)	16 (53.3%)	20 (50%)		

There was no significant distinction between all groups of study regarding neonatal characteristics just after delivery (P > 0.05) in all parameters (Table 2).

Table (2): Neonatal characteristics just after delivery between the all groups of study

		Group A (N=30)	Group B (N=30)	Group C (N=40)	F / χ^2	P
GA (weeks) Mean ± standard deviation		38.53 ± 1.01	38.43 ± 1.28	38.88 ± 0.992	1.61	.205
Birth weight (kg) Mean ± standard deviation		3.15 ± 0.323	3.11 ± 0.265	3.15 ± 0.337	.161	.851
Apgar at 1 min Mean ± standard deviation		7.13 ± 0.507	7.17 ± 0.461	7.05 ± 0.450	.578	.563
Apgar at 5 min Mean ± standard deviation		9.07 ± 0.521	8.63 ± 0.615	9.03 ± 0.577	**5.42**	**.006**
Mode of delivery	**CS**	18 (60%)	17 (56.7%)	27 (67.5%)	.927	.629
	VD	12 (40%)	13 (43.3%)	13 (32.5%)		

There was a significant distinction between all groups of study concerning respiratory rate, temperature, SBP, and DBP (P= 0.032, 0.001, 0.030 and 0.007 respectively) (Table 3).

Table (3): Vital signs distribution between the all groups of study

	Group A (N=30)	Group B (N=30)	Group C (N=30)	F	P
HR (beat/min) Mean ± standard deviation	136.1 ± 12.13	137.97 ± 15.04	137.18 ± 11.08	.164	.849
RR (cycle/min) Mean ± standard deviation	57.7 ± 7.96	63.23 ± 7.22	62.4 ± 10.23	**3.58**	**.032**
Temperature (ºC) Mean ± standard deviation	37.17 ± 0.26	37.12 ± 0.477	37.48 ± 0.366	**9.43**	**.001**
SBP (mmHg) Mean ± standard deviation	118.63 ± 8.67	119.93 ± 8.07	114.65 ± 8.98	**3.63**	**.030**
DBP (mmHg) Mean ± standard deviation	74.33 ± 3.71	77.8 ± 3.73	75.5 ± 4.87	**5.28**	**.007**

There was no significant distinction between the groups of study regarding echo parameters (P>0.05) in all parameters (Table 4).

Table (4): Echo parameters between the all groups of study

	Group A (N=30)	**Group B** (N=30)	**Group C** (n=40)	**F**	**P**
LVEF Mean ± standard deviation	70.77 ± 5.23	69.77 ± 2.58s	70.1 ± 3.24	.544	.582
LVFS Mean ± standard deviation	39.53 ± 3.42	38.37 ± 2.75	39.18 ± 3.45	1.03	.362
LVED Mean ± standard deviation	20.73 ± 3.18	19.18 ± 2.95	20.1 ± 2.24	2.37	.099
LVES Mean ± standard deviation	13.1 ± 2.54	13.42 ± 3.02	13.89 ± 2.51	.804	.451

LVFS (left ventricular fractional shortening), LVEF (left ventricular ejection fraction), LVES (left ventricular end-systolic), LVED (left ventricular end-diastolic pressure).

There was a significant reduction regarding expiratory positive airway pressure (EPAP) in the three groups. However, the reduction was better among group C compared to groups A & B (P<0.001) (Table 5).

Table (5): EPAP measurements between the all groups of study

PAP	**Group A** (N=30)	**Group B** (N=30)	**Group C** (n=30)	**F**	**P**
Baseline Mean ± standard deviation	55.1 ± 7.68	57.77 ± 7.49	56.8 ± 9.7	.760	.470
48 – 72 hours after Mean ± standard deviation	43.1 ± 7.53	52.5 ± 6.99	35.48 ± 5.33	**58**	**<0.001**
P value (within groups)	**P1 = 0.001**	**P2 <0.001**	**P3 <0.001**		
5 days after Mean ± standard deviation	42.4 ± 5.95	46.17 ± 7.57	27.53 ± 4.69	**95**	**<0.001**
P value (within groups)	**P1 =0.036**	**P2 <0.001**	**P3 <0.001**		
P*	**<0.001**	**<0.001**	**<0.001**		

p1: p value for comparing between group A and group B p2: p value for comparing between group A and group C p3: p value for comparing between group A and group C p*: repeated ANOVA test.

There was a significant distinction between the three groups according mean oxygen saturation (SPO_2) after 5 days (p<0.001). Moreover, there was a significant rise according SPO_2 in the 3 groups. However, the improvement was better among group C compared to groups A & B (p<0.001) (Table 6).

Table (6): SpO_2 measurements between the all groups of study

SpO_2 (%)	**Group A** (N=30)	**Group B** (N=30)	**Group C** (n=30)	**F**	**P**
Baseline Mean ± standard deviation	85.43 ± 9.09	83.7 ± 11.55	81.2 ± 11.17	1.38	.256
48 – 72 hours after Mean ± standard deviation	89.4 ± 7.97	88.77 ± 7.56	90.1 ± 5.85	.297	.744
5 days after Mean ± standard deviation	96.4 ± 3.29	94.87 ± 3.18	98.85 ± 0.427	**22**	**<0.001**
P value (within groups)	P1 =0.072	**P2 <0.001**	**P3 <0.001**		
P*	**<0.001**	**<0.001**	**<0.001**		

There was a significant distinction between the three groups of study according to time to response, ventilation duration, and inotropic agents (P<0.001) (Table 7).

Table (7): Clinical characteristics between the all groups of study

	Group A (N=30)	**Group B** (N=30)	**Group C** (N=30)	**F**	**P**
Time of response (days) Mean ± standard deviation	2.4 ± 0.675	3.57 ± 1.17	1.8 ± 0.687	**37**	**<0.001**
Ventilation duration (days) Mean ± standard deviation	4.33 ± 1.12	6.13 ± 1.68	3.23 ± 0.733	**51**	**<0.001**
Inotropic agents	13 (43.3%)	24 (80%)	13 (32.5%)	**16**	**<0.001**

Table (8) exhibited that hypotension incidence was significantly lesser among group C compared to the other groups (P=0.024). However, there was no significant distinction between the three studied groups concerning nausea/GIT disturbance (P=0.274), tachycardia (= 0.839) & bleeding manifestation (p=0 .212).

Table (8): Side effects distribution between the all groups of study

	Group A (S) (N=30)	**Group B** (N=30)	**Group C** (N=40)	**F**	**P**
Nausea/GIT disturbance	3 (10%)	5 (16.7%)	2 (5%)	2.6	.274
Tachycardia	2 (6.7%)	1 (3.3%)	2 (5%)	.351	.839
Hypotension	6 (20%)	10 (33.3%)	3 (7.5%)	**7.46**	**.024**
Bleeding manifestation	2 (6.7%)	4 (13.3%)	1 (2.5%)	3.1	.212

DISCUSSION

PPHN is a prevalent condition that is associated with a very high rate of illness and death [1]. The demographic characteristics analysis of the present research indicated that there were no statistically significant distinctions in gender & age between all groups (p > 0.05). In group S, the average age was 4.73 ± 2.68 years with 46.7% were men & 53.3% were females. In group M, the average age was 6.17 ± 4.04 years with 46.7% were males and 53.3% were females. In group C, the average age was 4.63 ± 2.16 years with equal distribution (50% males & 50% females). In a separate study conducted by **Al-lawama *et al.*** [7] the investigation comprised a total of twenty-seven neonates, whose ages ranged from twenty-eight to forty weeks. Out of the total of twenty-seven infants, seventeen were males (Sixty-three percent), while the remaining ten babies were females (thirty-seven percent). The average age at which PPHN was clinically diagnosed for the participants was two days, whereas the average age at which echocardiography confirmed the diagnosis was three days. The infant received an initial dosage of two hundred milligrams per kilogram of $MgSO_4$, followed by a continuous infusion at a rate of 50 mg/kg/h. Sildenafil was initiated following echocardiographic verification of PPHN. Sildenafil was administered to all infants diagnosed with PPHN. The first dosage was one milligram per kilogram administered at six-hour intervals.

Based on our research, there was no significant variation between the three groups in terms of neonatal characteristics, including gestational birth weight, age, Apgar score at one minute, & mode of delivery. A recent study conducted by **Huang *et al.*** [5] supports our findings, indicating that there was no statistically significant distinction observed among the groups studied (sildenafil plus magnesium sulfate versus magnesium sulfate) in terms of gestational age (weeks), birth weight (g), & delivery mode. The p-values for these variables were 0.286, 0.928, and 0.363 respectively.

Our findings indicated a notable disparity in respiration rate, temperature, SBP, and DBP across the three groups. The p-values were 0.032, 0.001, 0.030, and 0.007 respectively. **Imam *et al.*** [8] conducted an investigation to evaluate the effectiveness of sildenafil & milrinone as alternative treatments for PPHN. They found that both study groups demonstrated significant improvement in systolic pulmonary artery pressure & OSI values compared to the baseline values (P < 0.001).

The results of our research indicated that there were no statistically significant variances between the 3 groups in terms of echo parameters, involving left ventricular fractional shortening, LVEF, LVES, & LVED. Additionally, the severities of echo abnormalities discovered were 26.7%, thirty%, and thirty% in the related groups. In addition to our findings, a previous investigation conducted by **Kuntartiwi *et al.*** [9] demonstrated that sildenafil had no effect on the systolic function of the right heart. Furthermore, there were no significant variations in echocardiography results among the group that received sildenafil and the control group.

The current findings indicated a significant decline in EPAP across all three groups. Nevertheless, the decrease was more significant in group C (S + M) in comparison with groups S and M. Furthermore, the EPAP value was found to be lower in the S group compared to the M group. In a comparable investigation

entitled "$MgSO_4$ versus sildenafil in the treatment of PPHN", the EPAP of both groups demonstrated a significant reduction at forty-eight to seventy-two hours and five days following the initiation of either treatment in comparison with the baseline EPAP, as reported by **Shaltout *et al.*** [10]. There were no significant distinctions observed between the EPAP measurements of group S & group M at baseline (P1) & 48-72 hours (P2). Nevertheless, following five days of treatment, and group S exhibited a significantly reduced EPAP (P3) of 24.7 ± 3.8 millimeters of mercury than group M (36.2 ± 3.2 millimeters of mercury) (P = 0.012).

In comparison with groups S and M, group C exhibited a significant rise in SPO_2 after five days ($p<0.001$). In the magnesium sulfate group, the mean oxygen saturation (SPO_2) was 79.15% in the right hand & 68.58% in the left hand. While, in the magnesium sulfate plus sildenafil group, it was 79.92% in the right hand & 69.33% in the left hand. No statistically significant distinctions were observed amongst the two groups (p=0.215). This was demonstrated by **Abdalsalam *et al.*** [11].

The clinical characteristics revealed significant variations among the three groups under investigation in terms of inotropic agents, ventilation duration, & time to response. **Mandell *et al.*** [12] observed that the objective of mechanical ventilation is to enhance oxygenation by attaining "optimal" lung volumes that will reduce the possibility of long-term lung injury as a result of volutrauma, barotrauma, or atelectotrauma.

The frequency of hypotension was considerably lower in group C than in the other groups with respect to the distribution of side effects. Nevertheless, the remaining adverse effects (tachycardia, nausea, & bleeding manifestation) lacked any significant variation among the 3 groups. In a previous study, **Shaltout *et al.*** [10] discovered that twenty cases in group S developed hypotension (twenty percent) and four patients experienced hemorrhage (four percent). No one suffered diarrhea or rash. In group M, five neonates suffered central nervous system depression (five percent) & twenty developed hypotension (twenty percent). Hypocalcemia and GIT disturbances were not observed in any of the patients.

CONCLUSION

Magnesium sulfate and sildenafil are safe pulmonary vasodilators for PPHN treatment, serving as rescue therapy. Combining these drugs improved the recovery of newborns with persistent pulmonary hypertension, surpassing monotherapy with only $MgSO_4$ or sildenafil.

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