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Outcomes of Newborn Infants With Pulmonary Hypertension Treated With Oral Sildenafil

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Abstract

Background: Persistent pulmonary hypertension of the newborn (PPHN) is a disease with a high mortality rate. The incidence of PPHN is approximately 0.8 per 1,000 live births. Inhaled nitric oxide remains the treatment of choice, but in areas where inhaled nitric oxide is not available, sildenafil citrate is considered the best alternative vasodilator. We conducted this study to investigate the efficacy of oral sildenafil in treating neonatal pulmonary hypertension.

Methods: This is a retrospective study of all newborns diagnosed with PPHN who received oral sildenafil over an 8-year period.

Results: A total of 27 newborns were included in the study. The most common primary disease was respiratory distress syndrome. The mortality rate was 44.4%; all newborns with cardiovascular shock at presentation died.

Conclusions: Oral sildenafil is a promising medication that can help neonates with mild to moderate PPHN in hospital units where inhaled nitric oxide is not available. Development of a treatment protocol to standardize the care of such infants will positively impact outcomes.

Keywords: Neonate; Pulmonary hypertension; Oral sildenafil

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening neonatal syndrome, characterized by a failure of the normal circulatory transition. It results in marked pulmonary hypertension and hypoxemia secondary to right-to-left shunting of blood. PPHN has a high mortality rate [1], and can affect both term and preterm infants. Inhaled nitric oxide (iNO) remains the treatment of choice [2]. In areas where iNO is not available, sildenafil citrate is considered the alternative vasodilator of choice [3]. Sildenafil citrate is a selective and potent inhibitor of phosphodiesterase type 5 (PDE5) [4], which is a cyclic guanosine monophosphate (cGMP) specific degrading enzyme [4]. The inhibitory effect of sildenafil on PDE5 results in an increased level of cGMP, which enhances nitric oxide-mediated vasodilation [5]. Sildenafil has been used in both its parenteral and oral forms to treat PPHN [6, 7].

In Jordan, where nitric oxide and the parenteral form of sildenafil are not available, oral sildenafil remains the only option for treating PPHN. In our practice, whenever a newborn is diagnosed with PPHN, treatment starts with oral sildenafil and possibly magnesium sulfate.

The purpose of this study was to investigate the effectiveness of sildenafil when treating PPHN. In this paper, we report on the outcomes of neonates in our unit who were diagnosed with PPHN and subsequently treated with oral sildenafil as the primary treatment modality.

Materials and Methods

This is a retrospective study of all newborns diagnosed with PPHN who received oral sildenafil over an 8-year time period. It was conducted in a level-3 university hospital neonatal unit. The study was approved by the deanship of scientific research at the University of Jordan, and by the Ethical and Institutional Review Board (IRB) Committees at the University Hospital. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

All infants with pulmonary hypertension who received oral sildenafil and were admitted to our unit between the years 2008 and 2016 were included in this study. We retrospectively reviewed the charts of these newborns. Demographic and clinical data, and the results of laboratory and imaging studies were collected and recorded.

Clinical diagnosis of pulmonary hypertension was based on persistent hypoxemia despite ventilation with 100% oxygen, and a difference in oxygen saturation between the upper and lower limbs of ≥ 10% [8], which is usually seen in high-risk term or late preterm infants [9]. Echocardiography criteria for diagnosis of PPHN were based on both qualitative and

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quantitative assessment. Qualitative assessment was based on evidence of right-to-left shunting at either patent ductus arteriosus or patent foramen ovale, the presence of a flattening of the interventricular septum, or bowing into the left ventricle. Tricuspid valve regurgitation, when present, was used to quantitatively estimate pulmonary systolic pressure [10]. Systolic pressure > 40 mm Hg, or systolic pressure higher than systemic arterial pressure, was considered diagnostic of pulmonary hypertension.

Conventional ventilation was done via assisted ventilation mode. High-frequency oscillation ventilation (HFOV) was introduced during the last 2 years of the study. Dobutamine was started at a rate of 10 µg/kg/min. If hypotension was present, dopamine was added, with a starting rate of 10 µg/kg/min. Sedation was achieved by fentanyl with a starting dose of 1 µg/kg, followed by a continuous infusion with a dose of 1 µg/kg/h that was titrated according to the infant's response. If hypoxemia persisted, then magnesium sulfate was added after normalization of the blood pressure. The infant was given an initial dose of 200 mg/kg magnesium sulfate, which was then continuously infused at the rate of 50 mg/kg/h. Levels were observed every 6 h and were maintained between 3.5 and 5.5 mmol/L. Antibiotics were given only if there was suspicion of sepsis. Surfactant was administered according to the primary disease, and mainly to infants with respiratory distress syndrome, meconium aspiration, and those with diaphragmatic hernia.

Sildenafil was started after echocardiographic confirmation of PPHN. All infants diagnosed with PPHN received sildenafil. The starting dose was 1 mg/kg every 6 h. If the infant's condition worsened, the dose of sildenafil was increased to 2 mg/kg every 6 h. The solution was prepared from a 50 mg tablet, which was crushed and dissolved in distilled water. The required dose was given via nasogastric tube.

Follow-up echocardiography was usually performed after 24 h of sildenafil administration, with the frequency adjusted according to the newborn's clinical status.

Oxygen saturation was kept between 90% and 95%. Blood gases were measured frequently at the beginning of treatment; once the newborn stabilized, they were measured every 6 h. Serum electrolytes including calcium and bilirubin were measured at least once daily. In cases of severe hyperbilirubinemia, elevation of the direct bilirubin type, or prolonged hyperbilirubinemia, serum liver enzymes were measured. Partial thrombin and prothrombin time were measured only when there was evidence of bleeding or an elevation of the direct type of bilirubin. A complete blood count was performed every 2 - 3 days, or whenever there was a clinical indication. The hematocrit was kept above 40% while on mechanical ventilation.

The weaning stage began with a reduction in the dose of magnesium sulfate, and then of the inotropes. Sildenafil weaning started only after the infant was extubated. Surviving newborn infants went home on sildenafil, and parents were given instructions and a weaning schedule. A follow-up appointment with a cardiologist was arranged within 1 week of discharge.

Data are presented as numbers and frequencies. A Fisher's exact test was used to compare values between groups. P values ≤ 0.05 were considered statistically significant.

Table 1. Demographic Characteristics of Patients With Pulmonary Hypertension Who Received Sildenafil Treatment

Characteristics	
Mean gestational age (range), weeks	36 (28 - 40)
Cesarean section, N (%)	18 (66.7)
Male gender, N (%)	17 (63.0)
Birth weight, mean ± SD, g	2,800 ± 467
Small for age, N (%)	4 (14.8)
Apgar score	
First min (mean)	6
Fifth min (mean)	8
Intubation at delivery room, N (%)	9 (33.3)
Maternal age (mean), years	29
Maternal disease, N (%)	
Hypertension	1 (3.7)
Thrombophilia	4 (14.4)
Chorioamnionitis	1 (3.7)
Prolonged rupture of membranes	4 (14.4)

SD: standard deviation.

Results

Twenty-seven newborn infants were included in this study. During the study period, 35,000 live neonates were born in our hospital, making the incidence of PPHN 0.8 per 1,000 live births. The mean gestational age of participants was 36 weeks, with ages ranging from 28 to 40 weeks. Of the 27 infants, 17 were male (63%). The mean birth weight of participants was 2,800 ± 467 g.

Nine of the neonates (33.3%) were intubated at delivery (Table 1). Respiratory distress syndrome was the most common lung disease (37%), followed by congenital diaphragmatic hernia (18.5%, Table 2). Additionally, 29.6% of neonates presented with shock, and 44.4% of the infants required the administration of 100% O_2. The mean age of clinical diagnosis of PPHN for participants was 2 days, while the mean age of echocardiography confirmation was 3 days.

Twelve of the patients died, yielding a mortality rate of 44.4% (Table 3). There were no significant differences between survivors and non-survivors in the use of inotropic agents or the use of magnesium sulfate before and after starting sildenafil (Table 4). The only significant difference between survivors and non-survivors was the presence of cardiovascular shock at presentation. All eight newborns who presented with shock died ($P < 0.0009$, Table 5).

Discussion

In this study, we retrospectively reviewed the outcomes of neonates with PPHN who were treated with oral sildenafil. Although nitric oxide is the treatment of choice for PPHN [2], in Jordan and many other low resource countries where this

Table 2. Original Disease in Neonates With Pulmonary Hypertension

Original disease	N (%)
RDS	10 (37.0)
Diaphragmatic hernia	5 (18.5)
MAS	4 (14.8)
Congenital pneumonia	2 (7.4)
HIE	2 (7.4)
CHD	2 (7.4)
Sepsis	1 (3.7)
Air leak	1 (3.7)

RDS: respiratory distress syndrome; MAS: meconium aspiration syndrome; HIE: hypoxic ischemic encephalopathy; CHD: congenital heart disease.

therapy is unavailable, oral sildenafil is a promising alternative [11]. Many previous reports have evaluated the use of oral sildenafil in neonatal PPHN [7, 12, 13]. A Cochrane review that included five randomized studies investigating the use of oral sildenafil in neonatal pulmonary hypertension concluded that sildenafil is effective in decreasing mortality and improving oxygenation, especially in resource-limited settings [14]. Four of the studies investigated sildenafil as the primary therapy of PPHN. However, those included studies used variable sildenafil dosing regimens, ranging from 0.5 to 3 mg/kg [7, 13, 15-17]. It was therefore difficult to determine the ideal treatment dosage when treating and researching PPHN.

In this study, 27 newborn infants, with a mean gestational age of 36 weeks, were included; all of them had developed secondary PPHN. Respiratory distress syndrome was the most common underlying lung pathology among the neonates. This finding indicates the importance of additional lines of therapy in the management of neonatal PPHN, including the choices of both ventilation strategy and surfactant therapy [18]. High frequency ventilation is the ventilation method of choice in neonatal pulmonary hypertension [18]. In our unit, HFOV was introduced during the last 2 years of the study. However, we did not observe any difference in mortality rates between patients ventilated with HFOV versus those with a conventional ventilation mode. This might be explained by variations in the use of HFOV, as sometimes it was used as a rescue therapy in neonates after failure of conventional ventilation, and sometimes as the first-line ventilation therapy.

Table 3. Clinical and Outcome Data of Neonates With Pulmonary Hypertension Treated With Oral Sildenafil

Character	N (%)
Shock at presentation	8 (29.6)
100% O_2 need at presentation	12 (44.4)
Metabolic acidosis at presentation	14 (51.8)
Respiratory distress on day 1	24 (88.9)
Age of clinical diagnosis of (days)	2[a]
Age of echo diagnosis of (days)	3[a]
Conventional mechanical ventilation	26 (96.2)
HFMV	7 (25.9)
Surfactant	12 (44.44)
Mortality	12 (44.4)

[a]Mean. HFMV: high frequency mechanical ventilation.

Table 4. Treatment for Pulmonary Hypertension Offered to Neonates Before and After Sildenafil Treatment

Medication	Pre sildenafil	Post sildenafil	P value
Dopamine	11 (40.75)	16 (59.25)	0.178
Dobutamine	16 (59.25)	23 (85.18)	0.035
Epinephrine	2 (7.4)	4 (14.81)	0.390
$MgSO_4$	12 (44.4)	14 (51.85)	0.587

The use of inotropic agents and magnesium sulfate was not altered after commencing sildenafil therapy. Systemic vasodilatation and the resulting decrease in blood pressure could explain the need for inotropes while on sildenafil. Magnesium sulfate is the traditional agent used for treating pulmonary hypertension in our setting. The fact that sildenafil did not decrease the need for and use of magnesium sulfate might reflect the possibility of a decrease in the potency of oral sildenafil in pulmonary vessels.

The mortality rate in our cohort, unlike previous studies, was high [14]. Surviving neonates did not demonstrate any significant differences from non-survivors in gestational age, birth weight, or incidence of the primary disease. The only significant difference between neonates who survived and those who died was the presence of cardiovascular shock. All neonates who had shock at presentation died. The non-surviving infants might have been experiencing a more severe pulmonary hypertension that required a more potent vasodilator. Severe PPHN causes decreased systemic perfusion due to right ventricular failure, left ventricular compression and underfilling, as well as severe hypoxemia due to right-to-left shunting. This resulting decreased blood flow to the neonate's gastrointestinal (GI) tract, as the body tries to preserve adequate perfusion to vital organs, and the subsequent decreased GI absorption, directly affects the pharmacokinetics of oral sildenafil [19]. One can extrapolate that oral sildenafil might work as a nitric oxide alternative, but only in mild to moderate cases of PPHN. The studies that have reported lower mortality rates than our study were controlled trials. These trials included strict protocols for treatment and follow-up, which minimized variation in the management of these patients. The longer duration of this present study might also have affected our results, due to the plethora of changes that have occurred in neonatal care practice over the 8-year study period.

Conclusions

Oral sildenafil is a promising medication that can help neonates with mild to moderate PPHN in hospital units where iNO is not available. Oral sildenafil might be best used as an adjunctive therapy in neonatal pulmonary hypertension at this

Table 5. Comparison Between Survivors and Non-Survivors

Character	Deaths, N (%)	Survivors, N (%)	P value
RDS	5 (42)	5 (33)	0.706
MAS	2 (17)	2 (13)	1.0
CDH	4 (33)	1 (6)	0.139
Intubation at birth	3 (25)	5 (33)	0.695
Birth weight (g), mean ± SD	2,700 ± 529	2,926 ± 384	0.210
Preterm	4 (33)	5 (33)	1.0
C/S	7 (58)	10 (67)	0.706
Male	8 (67)	9 (60)	1.0
Shock	7 (58)	0 (0)	0.0009
HFMV use	5 (42)	2 (13)	0.185

RDS: respiratory distress syndrome; MAS: meconium aspiration syndrome; CDH: congenital diaphragmatic hernia; C/S: cesarean section; HFMV: high frequency mechanical ventilation; SD: standard deviation.

time. Its use as a primary treatment needs more investigation, in order to find the optimum dose regimen for treating PPHN. The development of a future treatment protocol to standardize the care of such infants will positively impact patient outcomes and likely decrease mortality rates and improves the quality of life among the neonatal population. This is a retrospective study; prospective studies are needed to investigate the use of sildenafil in neonatal pulmonary hypertension.

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Conflict of Interest

The authors have no conflict of interest to declare.

Informed Consent

Informed consent is not requested as this study is a retrospective chart review, and the study did not involve any identification of the patients.

Author Contributions

MA: idea, design and writing of the manuscript; EB: acquisition of data and approving final draft; AA: gathering data and analysis; RJ: gathering data and analysis; HA: gathering data and analysis; IA: design, analysis and writing of the manuscript.

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