The outcome of oral sildenafil therapy on persistent pulmonary hypertension of the newborn with respiratory distress

Esaad M. Monazea[a], Sahar S. Khattab[b], Asmaa A.W. Ebrahim[a], Layla A. Mohamed[c], Howayda A.A.R. Ahmed[a]

Background Persistent pulmonary hypertension (PPHN) is defined as failure of normal pulmonary vascular adaptation at or soon after birth, resulting in a persistent high pulmonary vascular resistance, which leads to diminished pulmonary blood flow and shunting of unoxygenated blood into systemic circulation through an opened foramen ovale and/or the ductus arteriosus. The prevalence of this syndrome is about 1.9/1000 in the population of neonates born at term.

Objective The aim was to evaluate the efficacy and safety of oral sildenafil in the treatment of PPHN.

Patients and methods This prospective interventional study was conducted on 50 neonates who were of more than or equal to 37 weeks gestational age and less than 3 days old and were diagnosed as PPHN by echocardiogram and had an oxygenation index (OI) more than or equal to 20. All included cases were given oral sildenafil as per the study protocol with a starting dose of 0.5–2 mg/kg/dose. OI, oxygen saturation, alveolar arterial oxygen gradient, and mean airway pressure were monitored serially.

Results This study showed a significant decrease in OI after 30 min of starting treatment and after 24 h of treatment in the studied cases 16.1±1.7 (P=0.010); also, there was a significant decrease in ESPAP? after treatment estimated by ECHO from mean 49.4±5,9 to 42.5±5.7 (P<0.001). Furthermore, this study showed a significant decrease in brain-type natriuretic peptide in studied cases after treatment with sildenafil.

Conclusion Oral sildenafil may be of benefit in improving oxygenation in infants with PPHN as it can effectively improve OI and reduce right ventricular systolic pressure.

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Departments of , [a]Pediatrics, [b]Clinical Pathology, [c]Cardiology, Faculty of Medicine, Al Azhar University, Cairo, Egypt

Correspondence to Howayda A.A.R. Ahmed, BSc, Department of Pediatrics, Faculty of Medicine, Al Azhar University, Cairo, 11788, Egypt.
Tel: 01140200115;
e-mail: howayda_arous1977@yahoo.com

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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a common problem in neonates with a high mortality rate. The survival rate has improved after the advent of high-frequency ventilation and inhaled nitric oxide. However, inhaled nitric oxide is expensive and unavailable in most neonatal centers [1].

PPHN occurs in as many as 1.9 of 1000 live births. Mortality is 10–20% in spite of high-frequency ventilation, surfactant, inhaled nitric oxide, and extracorporeal membrane oxygenation [2].

Aim

Our study aimed to evaluate the feasibility of using oral sildenafil and its effect on oxygenation in PPHN in term neonates with respiratory distress, and to estimate the possible risk factors and assess the outcome of these cases to prove that brain-type natriuretic peptide (BNP) as a marker is useful for the diagnosis of PPHN.

Patients and methods

This prospective study was carried out at the Neonatal Intensive Care Unit, El Mataria Teaching Hospital. The approval from the Research Ethics Committee of the Faculty of Medicine, Al-Azhar University was also obtained. It included 50 neonates admitted during the period from January 2015 to November 2016.

Written informed consents were taken from the legally authorized representatives of all participants after proper explanation of the study.

All cases were subjected to the following:

Full history taking

(1) Prenatal history:
   (a) Maternal medical history of any acute or chronic illness before or during pregnancy.
   (b) Maternal obstetric history including parity, gravidity, previous abortions, and mode of delivery.

(2) Natal history: delivery data, duration of labor, intrapartum maternal medications, Apgar score, efforts for neonatal resuscitation, and neonatal examination in the delivery room.
(3) Postnatal history including postnatal age, type of respiratory support, and duration of exposure to hyperoxia.

Clinical assessment

(1) Estimation of gestational age by the new Ballard score.[4]
(2) Anthropometric measurements (body weight, length, and skull circumference) and vital data (heart rate, respiratory rate, temperature, and blood pressure).
(3) Recording of ventilatory settings, mode, and duration of ventilation, daily mean FiO_2, and arterial blood gases.

Inclusion criteria

PPHN or hypoxemic respiratory failure associated wit: idiopathic PPHN, meconium aspiration syndrome, respiratory distress syndrome, sepsis or pneumonia in newborns of more than or equal to 37 weeks gestation. Age is less than 72 h at enrollment; moderate hypoxemic respiratory failure with 15<oxygenation index (OI)<25 (OI is calculated as FiO_2×mean airway pressure×100/postductal PaO_2), absence of structural heart disease (except patent ductus arteriosus, atrial septal defect <1 cm, or muscular ventricular septal defect <2 mm).

Exclusion criteria

First, profound hypoxemia (qualifying PaO_2 <30 mmHg from a blood gas drawn within 30 min of starting study drug infusion); second, hypotension (mean arterial pressure <35 mmHg); third, congenital heart disease (except patent ductus arteriosus, atrial septal defect <1 cm, or muscular ventricular septal defect <2 mm); fourth, congenital diaphragmatic hernia or lung hypoplasia syndromes (diagnosed on the basis of prolonged oligohydramnios); fifth, active seizures. Apgar score of less than 3 at 5 min or need for hypothermia treatment for neonatal encephalopathy; sixth, bleeding diathesis; seventh, lethal congenital anomaly.

Biochemical analysis: a blood sample was withdrawn within the first 24 h and on the second day of life and subjected to do complete blood count, C-reactive protein, electrolytes, and blood culture.

Chest and heart radiographic examination: for the assessment of cardiothoracic ratio, pulmonary vasculature, and any lung parenchymal lesions.

Echocardiography: was performed using Sonosite portable ultrasonic machine phase's array sector scanner with a 5 MH_Z probe. Systolic pulmonary artery pressure was estimated from the tricuspid valve noninvasively by continuous wave Doppler using the modified Bernoulli equation assuming the right atrial pressure to be 10 mmHg in the absence of right ventricular outflow obstruction [5].

Laboratory techniques: test principle for BNP; enzyme-linked immunosorbent assay is based on the competitive binding enzyme immunoassay technique. The microtiter plate provided in this kit has been precoated with an antibody specific to, during the reaction, in the sample or standard competes with a fixed amount of biotin-labeled for sites on a precoated monoclonal antibody specific to. Excess conjugate and unbound sample or standard are washed from the plate.

Statistical methods

Data were analyzed using IBM SPSS advanced statistics (Statistical Package for the Social Sciences), version 21 (SPSS Inc., Chicago, Illinois, USA). Numerical data were described as mean and SD or median and range. Categorical data were described as numbers and percentages. Data were explored for normality using Kolmogrov–Smirnov test and Shapiro–Wilk test.

Results

Table 1 shows increased percentage of cesarean section vs normal vaginal delivery (76 vs 24%); male babies were more than females (62 vs 38%) (Table 2).

Table 1 Demographic data of all studied cases

	Count (%)	Total (%)
PNA (days)		
1	42 (84)	50 (100)
2	8 (16)	
Mode of delivery		
CS	38 (76)	50 (100)
NVD	12 (24)	
Sex		
Female	19 (38)	50 (100)
Male	31(62)	
Birth weight (kg)		
Mean±SD	3.3±0.5	
Range	2–5	

CS, cesarean section; NVD, normal vaginal delivery; PNA, postnatal age.

Table 2 Maternal and obstetric risk of the studied cases

Maternal diseases and maternal drugs	*N* (%)
No risk factors	11 (22)
Preeclampsia	9 (18)
PROM	6 (12)
Antepartum hemorrhage	2 (4)
Gestational diabetes	13 (26)
Anemia	7 (14)
Polyhydramnios	1 (2)
Urinary tract infection	3 (6)
Oligohydramnios	2 (4)
Vaginal infection	1 (2)

PROM, premature rupture of membranes.

Table 4 Estimated pulmonary arterial pressures of the studied cases before and after sildenafil treatment

	Before (mean ±SD)	After (third day) (mean ±SD)	*P* value
Estimated pulmonary arterial pressures (mmHg)	49.4±5.9	42.5±5.7	<0.001

Table 6 Arterial blood gas parameters of the studied cases before and after sildenafil treatment

	Before (mean±SD	After (mean±SD)	*P* value
pH	7.32±0.09	7.38±0.08	<0.001
PCO_2 (mmHg)	49±12	43±9	0.001
HCO_3 (mmHg)	21.3±4.1	22.7±3.7	0.033
PO_2 (mmHg)	46±22	54±24	<0.001

Table 2 shows that only 22% of cases have no maternal risk factor ; 78% of cases showed risk factors and the most common is gestational diabetes (26%) followed by preeclampsia 18%. Thirty-nine out of 50 neonates (39/50) (88%) had a positive risk factor for PPHN, while 11/50 (22%) neonates were of normal vaginal delivery and had no history of risk factor developed PPHN of unknown cause (Table 3).

This table shows that the most common diagnosis of studied cases is respiratory distress (98%) followed by neonatal sepsis (34%) (Table 4).

This table shows there is a statistically significant decrease in the mean of estimated pulmonary arterial pressure after compared with before the treatment with sildenafil ($P<0.001$) (Table 5).

This table shows a significant decrease in OI after treatment compared with before treatment ($P<0.05$) (Table 6).

This table shows that there is a statistically significant increase in pH, HCO_3, and pO_2 level after sildenafil treatment compared with before treatment ($P<0.05$)

Table 3 Clinical diagnosis of the studied cases

	n (%)
Pneumonia	6 (12)
IDM	11 (22)
Sepsis	17 (34)
HMD	1(2)
TTN	11 (22)
MAS?	7 (14)
HIE	3(6)

HIE, hypoxic ischemic encephalopathy; HMD, hyaline membrane disease; IDM, infant to diabetic mother; MAS, meconium aspiration syndrome; TTN, tachypnea of the newborn.

Table 5 Comparison between oxygenation index before and after treatment with sildenafil in studied cases

	Mean±SD	*P* value
O_2 index before treatment	21.4±1.2	0.1
O_2 index 24 h after treatment	16.1±1.7	0.01
O_2 index 48 h after treatment	11.4±1.8	0.001

Table 7 Brain-type natriuretic peptide level of the studied cases before and after sildenafil treatment

	Before (mean±SD)	After (mean ±SD)	*P* value
Brain-type natriuretic peptide (pg/ml)	966.8±543.1	779.8 ±517.3	<0.001

Table 8 Descriptive data of the studied cases as regards the outcome

Outcome	*n* (%)
Improved	43 (86)
Died	7 (14)
Total	50 (100)

and a significant decrease in pCO_2 after treatment (Table 7).

This table shows that there is a statistically significant decrease in BNP level after treatment with sildenafil compared with before treatment ($P<0.05$) (Table 8).

This table shows the total numbers of improved and dead cases.

Discussion

Persistent PPHN results from the failure of relaxation of the pulmonary vasculature at birth, leading to shunting of nonoxygenated blood from the pulmonary into the systemic circulation. More often, full-term and near-term infants are affected; however, it is not uncommon to see PPHN in preterm infants who have respiratory distress syndrome [6].

In our study, maternal diseases such as uncontrolled diabetes mellitus (DM), hypertension, and anemia represented maternal risk factors in neonates. Uncontrolled DM is associated with high incidence of hyaline membrane disease, hypoglycemia, macrosomia, and fetal distress. This came in agreement with Lakshminrusimha and Keszler [9] who reported that maternal diseases play a role in the occurrence of PPHN especially DM, hypertension, and maternal anemia.

Sildenafil, which is currently approved for the treatment of erectile dysfunction, has emerged as a new promising therapeutic agent for the treatment of PPHN.

From different studies, it can be concluded that the time of maximum action and duration of the effect varies depending on the dose, the route of administration, and the clinical situation in which sildenafil has been used. The most used route of administration has been oral and the duration of the effect goes from 20 min to 6 h afterward [10].

In this study, pulmonary hypertension was more common in men (62% of cases vs 38% females). This was in agreement with Gijtenbeek and colleagues who conducted a study on 377 infants having PPHN and found that PPHN was more common in men (63.4 vs 36.6% females) . Human female neonates show enhanced lung maturation for similar gestational age than do men favoring postnatal adaptation and reducing the incidence of immaturity-associated lung conditions [11].

We found that neonates delivered by cesarean section [38 neonates (76%)] were associated with increased risk of developing pulmonary hypertension compared with those delivered vaginally [12 neonates (24%)]. This finding came in agreement with the results of Gijtenbeek and his colleagues who studied a cohort of all deliveries within a period of 23 months. From 9452 newborns, 8388 (88.7%) were delivered by cesarean section and 1064 (11.3%) were delivered vaginally [3].

In the current study, sepsis (34%) was the most common underlying diagnosis among cases with pulmonary hypertension (90%) and transient tachypnea of the newborn (14%); this was in partial agreement with Wang and others who reported that the most common underlying diagnosis associated with PPHN in their study was RD (40%), followed by pneumonia (20%) and meconium aspiration syndrome (20%) [14]. In contrast to our study, Stark and Eichenwald reported that meconium aspiration syndrome was the most frequent diagnosis among neonates with pulmonary hypertension in their study (42.1%), followed by primary PPHN (26.4%), RDS (17.4%), and pneumonia (13.7%) [7].

In our study, 100% of cases required inotropes in their management, which came in accordance with Thompson *et al.* [2] who demonstrated that all PPHN cases received dopamine for inotropes. Also Teng and Konduri [12] showed that inotropes were given to all or most patients who received MgSO4 and sildenafil for the treatment of PPHN.

In this study, different therapeutic modalities were effective in improving neonates with PPHN. All monitoring parameters such as oxygen saturation (SpO_2), capillary blood gases, and systolic pulmonary artery pressure had shown statistical improvement after initiation of conventional therapy. This was consistent with Thompson and others who studied the effect of different therapeutic modalities in the treatment of PPHN and they proved that there was improvement in oxygenation in all of the studied infants with time ranging between 6 and 30 h after initiation of treatment, and all infants showed a steady and significant improvement in SpO_2 over time [2].

This study showed a statistically significant decrease in estimated systolic pulmonary artery pressure measured by echocardiography after management of patients using sildenafil. Similar results were reported by Trottier-Boucher *et al.* [13] who conducted a retrospective study of oral sildenafil use in 23 term neonates with bronchopulmonary dysplasia-associated pulmonary hypertension in which oral sildenafil resulted in echocardiographic improvement in 15/21 neonates (71%), but there was clinical improvement in only 8/23 neonates (35%), mostly in the first 48 h. Sildenafil was started at a median chronological age of 28 days at an initial dose of 1 mg/kg/day (median dose 4.4 mg/kg/day).This study showed a statistically significant decrease in OI after administration of sildenafil. This was in accordance with Thompson *et al.* [2] and Lakshminrusimha and Keszler [8] who found that oral sildenafil in term/near-term infants with severe PPHN and severe hypoxemia improved OI and SpO_2 and did not cause systemic hypotension or noticeable adverse effects.

In this study, the mean BNP level of the studied cases was significantly decreased after sildenafil treatment compared with before treatment (966.8 pg/ml before

treatment vs 779.8 pg/ml after treatment). Similar results were reported by Shah *et al.* [15]. They found that BNP, a biomarker of cardiac ventricular strain, proved to be useful in evaluating the efficacy of PPHN treatment, and moreover, BNP helps to predict a rebound of PPHN.

Conclusion

Oral sildenafil may be of benefit in improving oxygenation in infants with PPHN, as it can effectively improve OI and reduce right ventricular systolic pressure.

So, it has been recommended that: first, increasing research and understanding of the pathology of these high-risk babies will allow more targeted therapies to be delivered to these subsets of newborns. Second, Sildenafil is one of the drugs used in the management of severe PPHN. Third, we recommend starting with 0.5 mg/kg/dose and increasing the dose to 2 mg/kg/dose according to the follow up to pulmonary pressure by echocardiography.

This study is limited by the fact of being a single-center analysis. Prospective studies with the objective of evaluating the different therapies including a significant number of patients will give much more information regarding therapeutic efficacy and survival.

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Conflicts of interest

There are no conflicts of interest.

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