



ORIGINAL ARTICLE

Efficacy of sildenafil in persistent pulmonary hypertension of the newborn.

Muhammad Naveed¹, Fazal ur Rehman², Khurram Shah Nawaz³, Farhan Zahoor⁴, Bushra Madni⁵, Muhammad Imran⁶

Article Citation: Naveed M, Fazal ur Rehman, Shah Nawaz K, Zahoor F, Madni B, Imran M. Efficacy of sildenafil in persistent pulmonary hypertension of the newborn. Professional Med J 2022; 29(4):516-520. <https://doi.org/10.29309/TPMJ/2022.29.04.6617>

ABSTRACT... Objective: To find out efficacy of sildenafil for the treatment of persistent pulmonary hypertension of the newborn (PPHN). **Study Design:** Observational study. **Setting:** Department of Neonatology, Sughra Shafi Medical Complex, Sahara Medical College, Narowal. **Period:** May 2020 to April 2021. **Material & Methods:** A total of 22 neonates of both genders with diagnosis of PPHN were enrolled during the study period. Demographic characteristic along with information about perinatal and postnatal characteristics were recorded among all neonates at the time of admission. X-ray chest were asked. Oral sildenafil was administered as 2mg/kg per dose thrice a day to all study cases and continued till extubation. Outcome was recorded on the basis of difference in FiO₂ need after initiating sildenafil, time required to get ventilator off or mortality. **Results:** Out of a total of 22 neonates, 13 (59.1%) were male. Majority of the neonates, 15 (68.2%) were term newborns. Mode of delivery was lower segment cesarean section in 17 (77.3%) cases. APGAR score at 5 minutes was between 7 to 10 in 13 (59.1%) newborns. There were 13 (59.1%) newborns who required immediate resuscitation following birth. Meconium aspiration syndrome was the commonest associated condition found among 8 (36.4%) neonates. As per echocardiographic findings, 13 (59.1%) neonates had severe PPHN, 5 (22.7%) moderate and 4 (18.2%) mild. Mean oxygenation index at the time of admission was noted to be 46+14. Inotropic support was administered to 19 (86.4%) cases. Mean length of neonatal intensive care unit was 15+5 days. Mortality was reported among 10 (45.4%) neonates. **Conclusion:** Oral sildenafil was found to be a promising option for the treatment of neonates having PPHN. Oral sildenafil was found to successfully improve oxygenation among neonates having PPHN.

Key words: Neonates, Oxygenation, Persistent Pulmonary Hypertension of the Newborn, Sildenafil.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is considered to be a life threatening condition and associated with high rates of mortality (10-20%) among both term and per-term newborns.¹ Incidence of PPHN is estimated to be approximately 2/1,000 live-births.^{2,3}

Assisted ventilation and the administration of inhaled nitric oxide (iNO) are considered to be the best approaches for the management of PPHN but iNO is not always freely available and is quite costly especially in resource-limited settings.^{4,5} Around 30% of patients treated with iNO do not respond to this treatment and might further need additional options like extracorporeal membrane oxygenation (ECMO).⁶ Respiratory distress syndrome is one of the most common underlying

lung pathology among the neonates indicating the importance of additional lines of therapy in the management of neonatal PPHN, including the choices of both ventilation strategy and surfactant therapy.^{7,8}

Sildenafil citrate is taken as a good alternative vasodilator with selective and potent inhibition of phosphodiesterase type-5 which is known to be a cyclic guanosine monophosphate (cGMP) degrading enzyme. Inhibitory effects of sildenafil result in raised levels of cGMP which improves nitric oxide mediated vasodilation.⁹ Sildenafil is available in both oral as well as parenteral form for the treatment of PPHN. Due to these reasons, sildenafil becomes a possible choice for the treatment of PPHN so we planned this study to find out efficacy of sildenafil for the treatment

1. FCPS (Pediatric Medicine), Senior Registrar Pediatrics, Sahara Medical College Narowal.
2. FCPS (Pediatric Medicine), Fellow Pediatric Cardiology, NICVD, Karachi.
3. FCPS (Pediatric Medicine), Associate Professor Pediatrics, Sahara Medical College Narowal.
4. FCPS (Pediatric Medicine), Assistant Professor Pediatrics, Fatima Jinnah Medical University/Sir Gangaram Hospital, Lahore.
5. FCPS (Pediatric Medicine), Assistant Professor Pediatric Medicine, Shalamar Medical and Dental College Lahore.
6. FCPS (Pediatric Medicine), Senior Registrar Pediatric Medicine, Sheikh Zayed Hospital, Rahim Yar Khan.

Correspondence Address:
Dr. Fazal ur Rehman
Department of Pediatric Cardiology,
NICVD, Karachi.
fazal171@gmail.com

Article received on: 27/05/2021
Accepted for publication: 02/09/2021

of persistent pulmonary hypertension of the newborn.

MATERIAL & METHODS

This observational study was conducted at The Department of Neonatology, Sughra Shafi Medical Complex, Sahara Medical College, Narowal, Pakistan from May 2020 to April 2021. Approval from Institutional Ethical Committee was taken for this study. Written consent was sought from parents/guardians of all study participants.

A total of 22 neonates of both genders with diagnosis of PPHN were enrolled during the study period. All neonates with congenital heart defects, lung hypoplasia or sepsis were excluded. Diagnosis of PPHN was made on the basis of pre-post ductal oxygen saturation > 15%, persistent hypoxia (PaO₂ < 50 mmHg) and need of 100% oxygen at the time of admission. Severity of PPHN was based on echocardiographic findings suggested as direction of shunt at ductus arteriosus and foramen ovale and tricuspid regurgitation flow velocity.

Demographic characteristic along with information about perinatal and postnatal characteristics were recorded among all neonates at the time of admission. X-ray chest were asked. Oral sildenafil was administered as 2mg/kg per dose thrice a day to all study cases and continued till extubation. Antibiotics, analgesics, sedation, inotropes along with suction was done among all cases. Oxygenation index was estimated as FiO₂xMAP/PaO₂ where FiO₂ is fraction of inspired oxygen, MAP is mean airway pressure and PaO₂ is the partial pressure of oxygen in arterial blood.¹⁰ Outcome was recorded on the basis of difference in FiO₂ need after initiating sildenafil, time required to get ventilator off or mortality. A specifically designed proforma was used for data entry while data was analyzed using SPSS version 26.0.

RESULTS

Out of a total of 22 neonates, 13 (59.1%) were male. Majority of the neonates, 15 (68.2%) were term newborns. Mode of delivery was lower segment cesarean section in 17 (77.3%) cases.

Apgar score at 5 minutes was between 7 to 10 in 13 (59.1%) newborns. There were 13 (59.1%) newborns who required immediate resuscitation following birth. Meconium aspiration syndrome was the commonest associated condition found among 8 (36.4%) neonates. Table-I is showing characteristic of all neonates enrolled in the present study.

Characteristics		Number (%)
Gender	Male	13 (59.1%)
	Female	9 (40.9%)
Gestational Age	Term	15 (68.2%)
	Pre-Term	7 (31.8%)
Mode of Delivery	Vaginal Delivery	5 (22.7%)
	Cesarean Section	17 (77.3%)
Apgar Score at 5 minutes	Good (7-10)	13 (59.1%)
	Poor (<7)	9 (40.9%)
Immediate Resuscitation required following birth		13 (59.1%)
Frequency of Clinical Features	Cyanosis	4 (18.2%)
	Apnea	1 (4.5%)
	Grunting	13 (59.1%)
	Tachypnea	14 (63.6%)
	Signs of Respiratory Distress	18 (81.8%)
	Bradycardia	4 (18.2%)
Associated Conditions	Respiratory Distress Syndrome	7 (31.8%)
	Meconium Aspiration Syndrome	8 (36.4%)
	Pneumonia	2 (9.1%)

Table-I. Demographic, maternal, prenatal and postnatal characteristics. (n=22)

As per echocardiographic findings, 13 (59.1%) neonates had severe PPHN, 5 (22.7%) moderate and 4 (18.2%) mild. Mean oxygenation index at the time of admission was noted to be 46+14. Inotropic support was administered to 19 (86.4%) cases. Mean length of neonatal intensive care unit was 15+5 days. No major adverse events were reported. Mortality was reported among 10 (45.4%) neonates. Table-II is showing severity of PPHN along with treatment and outcome data.

Treatment and Outcome Variables		Number (%)
Severity of PPHN	Mild	4 (18.2%)
	Moderate	5 (22.7%)
	Severe	13 (59.1%)
Mean oxygenation index at the time of admission (Mean+SD)		46+14
Mean airway pressure (Mean+SD)		19+6
Inotropic Support		19 (86.4%)
Sildenafil initiated at day of life (Mean+SD)		1.82+2.1
Sildenafil Stopped at day of life (Mean+SD)		14.8+4.2
Length of Neonatal Intensive Care Unit Stay (Mean+SD)		15+5
Outcome	Survived	12 (44.6%)
	Death	10 (45.4%)

Table-II. Severity of PPHN, treatment and outcome data. (n=22)

DISCUSSION

PPHN is known to be a disease with life-threatening outcomes.¹ Neonates usually present with critical illness and require initiation of immediate ventilation. As iNo and ECMO are not always available for treatment of PPHN in resource-limited settings, sildenafil is considered to possess good treatment outcomes. Researchers have presented sildenafil to improve oxygenation parameters among neonates having PPHN.^{11,12} In the present study, effectiveness of sildenafil was visible exhibiting decline in fractional inspiratory oxygen demand during the course of the treatment. Sildenafil was noted to be comparatively safe among our set of neonates as no major adverse events were noted during the treatment duration. A Cochrane review involving 5 randomized clinical trials revealed sildenafil to be effective in reducing mortality rates and improving oxygenation in PPHN especially in resource limited settings.¹³ Controversy exist regarding ideal dosage regimen of sildenafil for treating PPHN. In the present work, oral sildenafil was administered as 2mg/kg per dose thrice a day to all study cases and continued till extubation but different researchers have experimented with dosage regimens containing 0.5 to 3 mg/kg per dose in different clinical trials.^{14,15} No consensus exists on ideal dosage regimen for using oral sildenafil for the treatment of PPHN among neonates. A

recent local study evaluating sildenafil among 82 neonates with PPHN concluded sildenafil to be an effective option but those neonates who did not respond to sildenafil alone, combination of sildenafil with bosentan was noted to be useful.¹⁶

In the present study, meconium aspiration syndrome was found to be the most commonly associated morbidity (36.4%) among neonates and our findings are supported by Shekerdemian LS et al who also found meconium aspiration syndrome to be the most commonly associated condition among neonates with PPHN.¹⁷ Local data has revealed respiratory distress syndrome and meconium aspiration syndrome to be the commonest presenting associated conditions among neonates with PPHN.¹⁸ All these studies emphasize on the fact that meconium aspiration syndrome and respiratory distress syndrome are considered to be the most commonly associated conditions with neonates presenting with PPHN.

There were 10 (45.4%) neonates who reported mortality. A local study from Karachi¹⁸ has reported mortality rate of 33% among neonates with PPHN while a study from Jordan¹⁹ revealed mortality rate of 44.3%. All these studies elaborate that overall mortality among neonates with PPHN is very high.

There were some limitations of this study. As this was a single center study with comparatively small sample size, more studies involving multiple centers and larger sample size will further verify what is known about the effectiveness of sildenafil aiming treatment of PPHN in neonates. There was no comparator group or randomization in design so we were stuck to an observational design which has its own limitations. Further studies comparing sildenafil with other available alternatives should be conducted to further elaborate the effectiveness of different treatment modalities available for the treatment of PPHN in neonates.

CONCLUSION

Oral sildenafil was found to be a promising option for the treatment of neonates having PPHN. Oral sildenafil was found to successfully improve





oxygenation among neonates having PPHN.

Copyright© 02 Sep, 2021.

REFERENCES

1. Travadi JN, Patole SK. **Phosphodiesterase inhibitors for persistent pulmonary hypertension of the newborn: A review.** *Pediatr Pulmonol* 2003; 36(6):529–35.
2. Porta NF, Steinhorn RH. **Pulmonary vasodilator therapy in the NICU: Inhaled nitric oxide, sildenafil, and other pulmonary vasodilating agents.** *Clin Perinatol* 2012; 39(1):149–64.
3. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. **Persistent pulmonary hypertension of the newborn in late preterm and term infants in California.** *Pediatrics*. 2017; 139:e20161165.
4. Pedersen J, Hedegaard ER, Simonsen U, Krüger M, Infanger M, Grimm D. **Current and future treatments for persistent pulmonary hypertension in the newborn.** *Basic Clin Pharmacol Toxicol*. 2018 Oct; 123(4):392-406.
5. Nakwan N. **The practical challenges of diagnosis and treatment options in persistent pulmonary hypertension of the newborn: A developing country's perspective.** *Am J Perinatol*. 2018 Dec; 35(14):1366-1375.
6. Kelly LE, Ohlsson A, Shah PS. **Sildenafil for pulmonary hypertension in neonates.** *Cochrane Database Syst Rev*. 2017; 8(8):CD005494.
7. Martinho S, Adão R, Leite-Moreira AF, Brás-Silva C. **Persistent pulmonary hypertension of the newborn: Pathophysiological mechanisms and novel therapeutic approaches.** *Front Pediatr*. 2020; 8:342.
8. Walther FJ, Benders MJ, Leighton JO. **Persistent pulmonary hypertension in premature neonates with severe respiratory distress syndrome.** *Pediatrics*. 1992; 90:899–904.
9. Zhang W, Wu YE, Yang XY, Shi J, van den Anker J, Song LL, et al. **Oral drugs used to treat persistent pulmonary hypertension of the newborn.** *Expert Rev Clin Pharmacol*. 2020 Dec; 13(12):1295-1308.
10. Thomas NJ, Shaffer ML, Willson DF, Shih MC, Curley MA. **Defining acute lung disease in children with the oxygenation saturation index.** *Pediatr Crit Care Med*. 2010 Jan; 11(1):12-7.
11. Alnemri AM. **Black lung persistent pulmonary hypertension of the newborn. Saudi experience with sildenafil and nitric oxide.** *Saudi Med J*. 2017; 38(1):97-100.
12. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. **Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: A pilot randomized blinded study.** *Pediatrics*. 2006; 117(4):1077-1083.
13. Shah PS, Ohlsson A. **Sildenafil for pulmonary hypertension in neonates.** *Cochrane Database Syst Rev*. 2011; 8:CD005494.
14. Uslu S, Kumtepe S, Bulbul A, Comert S, Bolat F, Nuhoglu A. **A comparison of magnesium sulphate and sildenafil in the treatment of the newborns with persistent pulmonary hypertension: A randomized controlled trial.** *J Trop Pediatr*. 2011; 57(4):245-250.
15. Vargas-Origel A, Gomez-Rodriguez G, Aldana-Valenzuela C, Vela-Huerta MM, Alarcon-Santos SB, Amador-Licona N. **The use of sildenafil in persistent pulmonary hypertension of the newborn.** *Am J Perinatol*. 2010; 27(3):225-230.
16. Kamran A, Rafiq N, Khalid A, Amin F, Kumari V, Shaikh AS, et al. **Effectiveness of oral sildenafil for neonates with persistent pulmonary hypertension of newborn (PPHN): A prospective study in a tertiary care hospital.** *J Matern Fetal Neonatal Med*. 2021 May 12:1-7.
17. Shekerdemian LS, Ravn HB, Penny DJ. **Intravenous sildenafil lowers pulmonary vascular resistance in a model of neonatal pulmonary hypertension.** *Am J Respir Crit Care Med* 2002; 165(8):1098–102.
18. Hussain AS, Ali R, Ahmed S, Naz F, Haroon A. **Oral sildenafil use in neonates with persistent pulmonary hypertension of newborn.** *J Ayub Med Coll Abbottabad*. 2017 Oct-Dec; 29(4):677-680.
19. Al-Iawama M, Badran E, Abdelfattah AS, Jaddalla R, Almahameed HA, Al-Ammouri I. **Outcomes of newborn infants with pulmonary hypertension treated with oral sildenafil.** *Int J Clin Pediatr*. 2019; 8(2):27-31.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Naveed	Literature Review, Data collection.	
2	Fazal ur Rehman	Introduction, Proof Reading.	
3	Khurram Shahnawaz	Data Collection, Final Approval.	
4	Farhan Zahoor	Literature Review, Methodology.	
5	Bushra Madni	Data Analysis, Discussion.	Bushra Madni
6	Muhammad Imran	Drafting, References.	