CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3601263

Available online at: http://www.iajps.com Research Article

EFFICACY OF ORAL SILDENAFIL IN NEWBORNS HAVING PERSISTENT PULMONARY HYPERTENSION

Riaz Ahmed Shah, Muhammad Iqbal
Ziauddin Medical University

Article Received: November 2019 **Accepted:** December 2019 **Published:** January 2020

Abstract:
Every 7 out of 1000 live births experience Persistent pulmonary hypertension (PPHN). The rate of deaths is high but is reduced to around 15% with the use of inhalation of nitric oxide, surfactant and ventilation of the high frequency type. Selective decrease in the pulmonary vascular resistance is achieved with Sildenafil, which is a phosphodiesterase inhibitor of kind. The best to treat neonates suffering from hypertension of the pulmonary type is inhalation of nitric oxide including vasodilator of the pulmonary type. Sildenafil taken orally is a good prospective solution to the problem but it hasn't been methodically assessed in babies with PPHN.
***Material & Methods**: All patients who fulfilled the inclusion criteria and visited to department of pediatrics, Ziauddin University Hospital, Karachi were included in the study. Informed consent was taken from parents / guardian after explaining the procedure, risks and benefits of the study. Sildenafil tablet (50 mg) was crushed and reconstituted with distilled water and then stored in a plastic container in a refrigerator at 5°C. Oral sildenafil was given as per study protocol with a starting dose of 0.5 mg/kg/dose and increased by 0.5 mg/kg/dose to a maximum of 2 mg/kg/dose after assessing every 6 h if non-responsive. OI, oxygen saturations (SpO), alveolar-arterial oxygen gradient (A-aDO2), a/A ratio, and SOPI (for non-invasive ventilated babies) were monitored serially every 6 hours.*
***Results**: Mean ± SD of gestational age was 38.5±8.39 with C.I (37.4 to 39.5) weeks. Mean ± SD of birth weight was 3215±348 with C.I (3172.8 to 3257.1) grams. Efficacy of oral sildenafil was noted in 208 (78.78%) patents while 56 (21.22%) was found to be non-effective (P-value<0.001*).*
***Conclusion:** It is to be concluded that the efficacy of oral sildenafil in maintenance of persistent pulmonary hypertension was found to be effective and underscores the need for a large, controlled trial.*
***Keywords:** Neonates, Oral Sildenafil, Efficacy, Persistent pulmonary Hypertension.*

Corresponding author:
Riaz Ahmed Shah,
Ziauddin Medical University

QR code

Please cite this article in press Riaz Ahmed Shah et al., ***Efficacy Of Oral Sildenafil In Newborns Having Persistent Pulmonary Hypertension.,*** *Indo Am. J. P. Sci, 2020; 07(01).*

INTRODUCTION:

Serious failure of the respiratory system and hypoxemia are the characteristics of a physical condition called Persistent pulmonary hypertension(1, 2). Persistent pulmonary hypertension is associated with high rates of mortality and morbidity occurring in about 2 for every 1000 births around the globe(1). Although positive developments have taken place to treat PPHN, it still remains a deadly disease particularly in low income countries around the world who don't have the necessary resources(1). Walsh-Sukys et al.(1) documented a total mortality rate of 11% with the overall range between 5% and 32%) in a combined analysis conducted across the United States of America. Razzaq et al(3). documented a mortality rate of 25% at Multan Children's Hospital in Pakistan and Abdel et al.(4) documented a mortality rate of 22% at Al-Minya University Hospital in Egypt.

The occurrence of PPHN through various findings in South Africa was documented to be around 1% with a high rate of mortality ranging from 25% to 3% and 48% at Chris Hani Baragwanath Hospital as documented by Velaphi et al(5).

Due to its association with high rates of mortality and morbidity in the past, Persistent pulmonary hypertension of the newborn (PPHN) is considered as a very problematic neonatal illness. This illness is caused by the inability of the newborn to make a postnatal move from a high resistance fetal pulmonary state to a less resistant pulmonary circulation(4, 6).

PPHN is a neonatal serious condition categorized by a shared pathophysiological structures involving continuous raise of pulmonary vascular resistance and hypoxemia because of the right-to-left additional pulmonary thrusting of the flow of blood through the ductus arteriosus(7). PPHN impacts 2-6/1,000 of live births or around 1 in 10 of combined newborns disclosed to intensive care of the neonatal type and is complemented with a 7-9% danger of mortality including substantial morbidity(4).
The physiologic results of PPHN might originate with relation to a vast array of disorders including but not limited to congenital diaphragmatic hernia (CDH), asphyxia, pneumonia, meconium aspiration and se sepsis(7)

The best to treat neonates suffering from hypertension of the pulmonary type is inhalation of nitric oxide including vasodilator of the pulmonary type. Besides the treatment mentioned above, there are other ways to treat hypertension including bosentan, milrinone, magnesium sulfate, sildenafil and epoprostenol. Regardless, it must be noted that these methods of treatment are particularly proscribed in treating neonatal hypertension(8). Sildenafil yields vasodilatation by growing cyclic guanosine monophosphate (cGMP) by the reticence of the phosphodiesterase included in the dilapidation of cGMP to guanosine monophosphate(9, 10).

The goal of these methods of treatment is to decrease pulmonary vascular resistance, regulate blood pressure, inverse right to left shunt, and better arterial O2 saturation(7). In both models of the humans and animals, it has been proven that the use sildenafil is able to decrease resistance in the pulmonary vascular vein.

To treat pulmonary arterial hypertension and to better the ability to work out and in delaying physical detrimentation in people of old age, sildenafil has been regulated by the US Food and Drug Administration (FDA)(11, 12).

The goal of our analysis is to categorically find the initial data with relation to the viability of administering oral sildenafil and its impact on babies' oxygenation suffering from PPHN. The treatment of newborns in Pakistan remains a dire issue due to the lack of nitric oxides availability, which is the main way for its treatment. Since sildenafil is readily present in Pakistan, this study will focus on its use for treating PPHN in a local setting. Therefore, this study will help establish sildenafil as treatment modality for PPHN locally.

DATA COLLECTION:

A total of n=264 consecutively newborns having persistent pulmonary hypertension were recruited in the study was conducted at Department of Paediatric Medicine, Ziauddin University Hospital, Karachi, Pakistan after approval from institutional ethical review committee (ERC). Echocardiography (ECHO) was used to screen all newborns entering neonatal intensive care and after they fulfilled the predefined criteria, they were induced in the study following signed permissions from the family. Those Neonates of gestation age 35-42 weeks with (PAP) on ECHO >25 mm of Hg were included in the study. Neonates with Hyaline membrane disease diagnosed by clinical features and X-ray findings or having any congenital heart diseases are excluded from the study. Those Infants of >42 weeks with mild respiratory disease were also excluded.

A 50 mg tablet of was turned into powder form and reconstructed with purified water and then placed in a plastic bottle to be refrigerated at 5°C. Sildenafil was then orally administered as defined previously in the protocols of the study with the first dose of 0.5 mg/kg/dose and gradually augment

by another 0.5 mg/kg/dose to a total of 2 mg/kg/dose after evaluating each six hours if the patient was non responsive.

The criteria for eligibility included all newborns born in the range of 34 to 42 weeks gestational age. OI, oxygen saturations (SpO), alveolar-arterial oxygen
gradient (A-aDO2), a/A ratio, and SOPI (for non-invasive ventilated newborns) were observed consecutively each six hours. To evaluate the PAP, ECHO was conducted earlier and each 6 hours after the administration of sildenafil.

Separate evaluations were conducted for all newborns regardless if they were noninvasive ventilated or invasive.

A 50 mg tablet of was turned into powder form and reconstructed with purified water and then placed in a plastic bottle to be refrigerated at 5°C. Sildenafil was then orally administered as defined previously in the protocols of the study with the first dose of 0.5 mg/kg/dose and gradually augment byanother 0.5 mg/kg/dose to a total of 2 mg/kg/dose after evaluating each six hours if the patient was non responsive. According to their predefined standard criteria the effectiveness were evaluated was considered effective if at least 2 out of the three indicators are present from the baseline values like 1) SaO2>10% increase in ABG from baseline, 2) OI decreases by 10-20% from the baseline, 3) Decrease in FiO2 by 5-10% from the baseline PPHN. Pulmonary hypertension (PPHN) considered presence when the following criteria satisfied like 1) PAP > 25 mmHg, 2) PO2< 80 mmHg, 3) SPO2 < 90% at 100% respectively. Frequency and percentage was computed for qualitative variables like gender, cesarean section, and efficacy. Mean±SD was calculated for quantitative variable i.e. gestational age, birth weight, apgar score at 1 and 2 min, peak inspiratory pressure, peak end expiratory pressure, airway pressure, rate, inspired oxygen, duration of time, FiO2, PaCO2, PaO2, HCO3, A- aDO2 and Oxygen Indices. The stratification was done according to gender, gestational age, birth weight, and Apgar score to see the effect of these modifiers on outcome using Chi-square test/Fisher exact test. P value <0.05 was considered as significant in all analysis.All analysis were performed in SPSS-21.

Confidentiality about the patient's particulars was ensured. All the cases/subjects were entered on the proforma by their MR number and a separate study ID number were assigned to each case and it were used during further analysis. Patients name were not mentioned at any stage the data were kept confidential with primary investigator and were not be shared with anyone else. Data were stored in password protected computer with principal investigator. The entire evaluation of the patients, diagnostic tests and treatment were at the discretion of treating pediatric physician.

RESULTS:

In this study 264 patients were included to the efficacy of oral sildenafil in newborns having persistent pulmonary hypertension and the results were analyzed as the average maternal age of the mother was 38.5±8.39 with C.I (37.48 to 39.51) years. Mean birth weight of neonatal baby was 3215±348 with C.I(3172.8to 3257.1) grams in contract Apgar score at one and two minute reading was 6.48±1.25 with C.I (6.3 to 6.63) & 6.56±1.34 with C.I (6.39 6.72). In this study, sildenafil was not effective in 21.22% newborn patients with severe PPHN, 5 newborn were transferred to another center for iNO and/or ECMO and one newborn died with sepsis. significant improvement of oxygenation after sildenafil treatment was indicated by a significant reduction of oxygenation index (OI) s and increase of PaO2 ranging from 34.9 ± 9.6 to 13 ± 3.2 ($p < 0.001$), 42.4 ± 13.5 to 78 ± 11.5 (<0.01), and reduction of FiO2 from 1.22±0.45 to 0.3±0.06. Reduction of OI was more significant in post-hoc analysis after the 3rd and 4th doses of sildenafil i.e. from 18 to 24 hours from the start of treatment. Similarly mean peak inspiratory pressure was 33.2±5.1 & peak end expiratory pressure was observed 4.2±0.75 with C.I (4.10 to 4.29) respectively. Out of 264 patients 114 (56.81%) were male and 150 (43.19%) were female. Female are more predominant in this study. Cesarean section was documented in 76(28.78%) patients. Efficacy of oral sildenafil was noted in 208 (78.78%) patents while 56 (21.22%) was found to be non-effective as shown in **Chart#1.**

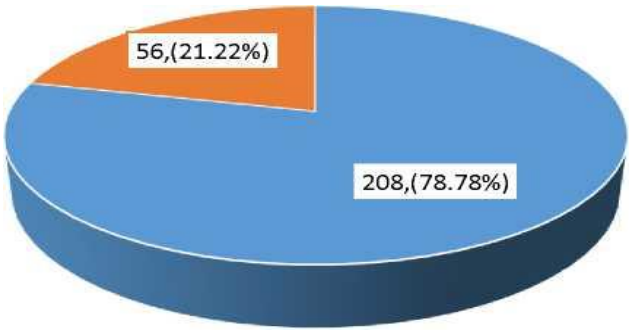
Table 1: Descriptive Statistics of demographics and babies characteristics at time of entry

Descriptive statistics	Mean±SD	95% C.I.
Gestational Age in (Weeks)	38.5±8.39	(37.4 to 39.5)
Birth weight in (Gram)	3215±348	(3172.8 to 3257.1)
Apgar Score at 1 Min	6.48±1.25	(6.32 to 6.63)
Peak Inspiratory Pressure (cm H20)	6.56±1.34	(6.39 to 6.72)
Peak End Expiratory Pressure (cm H20)	4.2±0.75	(4.1 to 4.29)
Inspired Oxygen	19.2±4.2	(18.69 to 19.7)
Airway Pressure (cm H20)	1.34±0.72	(1.25 to 1.42)
Rate (beats/min)	42.2±5.4	(41.5 to 42.8)
FIO2 in Days	2.7±1.6	(2.5 to 2.89)
Duration of Treatment	1.22±0.45	(1.16 to 1.27)
PaCo2	34±8.2	(33 to 34.9)
HCO3	34.2±12.48	(32.6 to 35.7)
PaOz	19.1±2.9	(18.7 to 19.4)
A-aDOz	42.5±7.48	(41.6 to 43.4)

Table 2: Comparison of efficacy of sildenafil among demographics and study characteristics

Study Characteristics	EFFICACY		P-Value
	Yes	No	
Gestation Age (Weeks) **35-—39** **>39**	150 (56.8%) 58 (22.0%)	30 (11.4%) 26 (9.8%)	0.008
Gender **Male** **Female**	105 (39.8%) 103 (39.0%)	45 (17.0%) 11 (4.2%)	<0.001*
Birth Weight (gm) **100-300 gm** **>3000**	72 (27.3%) 136 (51.5%)	40 (15.2%) 16 (6.1%)	<0.001*
Apgar Score at 1 (min) **3-5** **>5**	60 (22.7%) 148(56.1%)	42 (15.9%) 14 (5.3%)	<0.001*
Apgar Score at 2 (min) **3-5.5** **>5.5**	72 (27.3%) 136 (51.5%)	38 (14.4%) 18 (6.8%)	<0.001*

Chart 1: Stratification of Gestation Age Group with Efficacy (N=264)



DISCUSSION:

The strict criteria for including and excluding newborns in the study made it a strong one. The strength of the study was further enhanced by the use of successive sampling which was perfectly suited in conducting the study. Furthermore any bias in the study was reduced by using definitions that were objective for predicting and outcome variables. The chief confines of our analysis was the use of a substandard study plan case series the analysis and power of indication of which is inadequate and ergo. No calculation of the prior sample size is required for a successful conduct of this study.

Measurement of oral sildenafil in newborns to measure the effectiveness having (PPHN) has been significantly varied range of severity. There were a cumulative effect for multiple dosing; oxygenation further improved with each dose of sildenafil. Sildenafil causes pulmonary vasodilatation by increasing the availability of cGMP(11). In this study, a significant improvement of oxygenation after sildenafil treatment was indicated by a significant reduction of oxygenation index (OI) s and increase of PaO2 ranging from 34.9 ± 9.6 to 13 ± 3.2 ($p < 0.001$), 42.4 ± 13.5 to 78 ± 11.5 (<0.01), and reduction of FiO2 from 1.22±0.45 to 0.3±0.06. Reduction of OI was more significant in post-hoc analysis after the 3rd and 4th doses of sildenafil i.e. from 18 to 24 hours from the start of treatment. Data on the use of sildenafil in PPHN is currently very scarce with a few published case reports (12-15). Prospective randomized studies were all pilot in nature with a limited number of patients(1, 16). Our results were comparable to Herrera et al.(17) who also reported a significant improvement in OI in a group of infants who received sildenafil compared to a control group. Treatment groups had greater PaO2 at 72 hours and shorter duration of ventilation. In line with this study, Baquero et al.(18) conducted a pilot randomized blinded study in infants with severe PPHN with OI >25 who received oral sildenafil. In the treatment group, OI improved in all infants within 6 to 30 hours, with a steady improvement in sildenafil group as regards to O2 saturation, and in mortality. Similar results were reported in a couple of non- randomized reports (3, 18, 19).

In this study, sildenafil was not effective in 21.22% newborn patients with severe PPHN, 5 newborn were transferred to another center for iNO and/or ECMO and one newborn died with sepsis. The low mortality rate among patients treated with sildenafil in our study was comparable to those reported by Baquero et al.8 and by Shaltout et al(4). However; it cannot be concluded that oral sildenafil improve survival of PPHN patients since we did not conduct a randomized trial. In this study, sildenafil was well tolerated in newborn patients with no short term side effects for sildenafil particularly systemic hypotension as shown by non-significant difference of mean blood pressure between pre and post-sildenafil patients ($p = 0.63$); as it was reported by other studies(18, 19). A Cochrane meta-analysis study was conducted by Shah and Ohlsson(20) to measure the effectiveness sildenafil in the treatment of PPHN .It was found that sildenafil was safe, effective, and easily administered.

CONCLUSION:

We conclude that oral sildenafil could be a promising pulmonary vasodilator and effective for improving oxygenation in newborns with PPHN, particularly in medical facilities without iNO or ECMO. It was well tolerated and was not associated with short term side effects. Large multicenter randomized controlled studies are recommended to determine the long term safety and neuro developmental outcomes of infants receiving this treatment. In our study gestational age was 38.5±8.39 weeks and birth weight was 3215±348 grams. Efficacy of oral sildenafil was noted in 78.78% patents while 21.22% was found to be non-effective. Our results are comparable with most of national and international studies.

Strength & Weakness and Recommendation:

The study was further affected by the lack of outcome variables available in the study. Many factors with a direct connection to predictor and

outcome variables were not included in the study which further weakened the strength of our study. Generalizations could also not be made since we use sampling that was non probable. Regardless, this was mitigated by the small number of newborns being tested including the fact that the durations of the follow ups were succinct.

Since this study was conducted in a hospital setting, the findings do not truly represent the accurate frequency and extremity of the disease. Furthermore, generalizations cannot be made since this study was performed in one single unit of a hospital.

REFERENCES:

1. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. 2000;105(1):14-20.
2. Lakshminrusimha S, Kumar VH. Diseases of pulmonary circulation. Pediatr Crit Care. 4 ed ed: Elsevier Inc.; 2011. p. 632-56.
3. Razzaq A, Quddusi AI, Nizami N. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pak J Med Sci. 2013;29(5):1099.
4. Mohsen AHA, Amin AS. Risk factors and outcomes of persistent pulmonary hypertension of the newborn in neonatal intensive care unit of Al-Minya University Hospital in Egypt. J Clin Neonatol. 2013;2(2):78.
5. Velaphi S, Van Kwawegen A. Meconium aspiration syndrome requiring assisted ventilation: perspective in a setting with limited resources. J Perinatol. 2008;28(S3):S36.
6. Thérèse P. Persistent pulmonary hypertension of the newborn. Paediatr Respir Rev. 2006;7:S175-S6.
7. Prithviraj D, Reddy B, Shetty A, Deepthi, Reddy R. Oral Sildenafil in Persistent Pulmonary Hypertension of the Newborn in Invasive and Non-invasive Ventilated Babies-its Effect on Oxygenation Indices. Intern J Scient Stu. 2016;4(2):203-9.
8. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. Cochrane Database of System Rev. 2017(8).
9. Bajraktari G, Burhenne J, Bugert P, Haefeli WE, Weiss J. Cyclic guanosine monophosphate modulates accumulation of phosphodiesterase 5 inhibitors in human platelets. Biochem Pharmacol. 2017;145:54-63.
10. Kass DA. Cardiac role of cyclic-GMP hydrolyzing phosphodiesterase type 5: from experimental models to clinical trials. Curr Heart Fail. 2012;9(3):192-9.
11. Perez KM, Laughon M. Sildenafil in term and premature infants: a systematic review. Clini Thera. 2015;37(11):2598-607.
12. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148-57.
13. Agha H, El Tantawy A, Iskander I, Samad AA. Impact of Management Strategies on the Outcome of Persistent Pulmonary Hypertension of the Newborn. Cardiol Cardiovasc Med. 2017.
14. Khorana M, Yookaseam T, Layangool T, Kanjanapattanakul W, Paradeevisut H. Outcome of oral sildenafil therapy on persistent pulmonary hypertension of the newborn at Queen Sirikit National Institute of Child Health. J Med Assoc Thai. 2011;94:S64-73.
15. Sayed A, Bisheer N. Outcome of oral sildenafil in neonatal persistent pulmonary hypertension of non-cardiac causes. J Neonat Perinat Med. 2015;8(3):215-20.
16. Kahveci H, Yilmaz O, Avsar UZ, Ciftel M, Kilic O, Laloglu F, et al. Oral sildenafil and inhaled iloprost in the treatment of pulmonary hypertension of the newborn. Pediatr Pulmonol. 2014;49(12):1205-13.
17. Torres RH, González PC, Castillo JH, Gutiérrez RGL, Rodríguez Balderrama I. Sildenafil oral como alternativa en el tratamiento de recién nacidos con hipertensión pulmonar persistente. Rev Mex Pediatr. 2006;73(4):159-63.
18. 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. Pediatr. 2006;117(4):1077-83.
19. Agrawal A, Agrawal R. Persistent pulmonary hypertension of the newborn: Recent advances in the management. Int J Clin Pediatr. 2013;2(1):1-11.
20. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Cochrane Database Syst Rev. 2011;8(8):5494.