Original Article

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Oral Sildenafil in Persistent Pulmonary Hypertension of the Newborn in Invasive and Non-invasive Ventilated Babies-its Effect on Oxygenation Indices

Dinakara Prithviraj[1], Bharath Reddy[2], Abhijitshetty[3], Deepthi[3], Radha Reddy[3]

[1]Associate Professor, Department of Pediatrics, Vydehi Institute of Medical Sciences, Bengaluru, Karnataka, India, [2]Assistant Professor, Department of Pediatrics, Vydehi Institute of Medical Sciences, Bengaluru, Karnataka, India, [3]Junior Resident, Department of Pediatrics, Vydehi Institute of Medical Sciences, Bengaluru, Karnataka, India

Abstract

Background: Persistent pulmonary hypertension of the newborn (PPHN) is a common problem in the neonates with a high mortality rate.

Objective: To evaluate the feasibility of using oral sildenafil in invasive and non-invasive ventilated babies with PPHN and its effect on oxygenation in PPHN.

Design: This is a prospective observational case study conducted during January 2008 and January 2016 admitted in neonatal intensive care unit of Vydehi Institute of Medical Sciences with PPHN on invasive or non-invasive ventilated babies (resource-limited setting). All infants >32 weeks gestational age who were diagnosed as PPHN by echocardiogram and had an oxygenation index (OI) ≥20 were included in the study. Oral sildenafil was given as per study protocol with a starting dose of 0.25-0.5 mg/kg/dose and increased after assessing every 6 h if non-responsive. OI, oxygen saturations, alveolar-arterial oxygen gradient, a/A ratio, and saturation oxygen distending pressure index (for non-invasive ventilated babies) were monitored serially every 6 h. The main outcome variable was the effect of oral sildenafil on oxygenation indices. Sildenafil was discontinued when OI was <15 or if there was no significant change in OI after 8 doses.

Results: A total of 397 babies had PPHN of which 187 included in study. 167 babies were on invasive ventilation and remaining was on continuous positive airway pressure. There were a significant improvement pulmonary artery pressures with an improvement in OI in both ventilated and non-ventilated babies. 32 babies included in the study died during or after the study period of various causes related to the disease process.

Conclusion: Oral sildenafil was administered easily and tolerated improved OI in infants with severe PPHN, which suggests that oral sildenafil may be effective in the treatment of PPHN. Further studies are needed to assess the pharmacokinetics, efficacy and long-term side effects of this drug.

Key words: Persistent pulmonary hypertension, Sildenafil, Echocardiogram, Oxygenation index

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a neonatal emergency characterized by a common pathophysiological features including sustained elevation of pulmonary vascular resistance and hypoxemia due to the right-to-left extrapulmonary shunting of blood flow across the ductus arteriosus. PPHN affects 2-6/1,000 of live births or approximately 10% of all infants admitted to neonatal intensive care and is accompanied by an 8-10% risk of death and significant short- and long-term morbidity.[1] The physiologic findings of PPHN may be found in association with a wide range of cardiopulmonary disorders such as meconium aspiration, sepsis, pneumonia, asphyxia, congenital diaphragmatic hernia (CDH), respiratory distress syndrome, and others. Pathological

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Corresponding Author: Dr. Dinakara Prithviraj, Department of Pediatrics, Vydehi Institute of Medical Sciences, Bengaluru, Karnataka, India. Phone: +91-9742274849. E-mail: drdinakar.nishanth@gmail.com

findings include pulmonary vascular remodeling and smooth muscle hyperplasia, often in the absence of significant lung parenchyma pathology.[2]

PPHN can largely be thought of as one of four types:[3]

1. Persistent pulmonary vasoconstriction which is the most common type and seen in meconium aspiration syndrome (MAS), respiratory distress syndrome, pneumonia and sepsis
2. Functional vascular bed obstruction of pulmonary vessels seen in polycythemia
3. Decreased pulmonary vascular bed seen in pulmonary hypoplasia and CDH
4. Pulmonary venous hypertension seen in congenital heart diseases like total anomalous pulmonary venous connection.

The pathophysiology of each type is dependent on the point in gestation when the normal transition to extrauterine life fails. Thus, since the underlying pathophysiology differs, different pulmonary vasodilators may be more or less successful for the treatment and a thorough understanding of the pathways that are disrupted in each condition will be key to determine the most appropriate therapy.[3]

A variety of treatment options include hyperventilation, pressor agents, surfactant, sedation, alkalinization, vasodilatation (e.g., tolazoline, inhaled nitric oxide (NO), magnesium sulfate, adenosine, and sildenafil), and extracorporeal membrane oxygenation (ECMO). The aim of the treatment is to lower pulmonary vascular resistance, maintain systemic blood pressure, reverse right to left shunt, and improve arterial oxygen saturation. There is strong evidence for the use of inhaled NO and ECMO in the treatment of PPHN. However, many developing countries and resource-limited centers do not have the funds or the technical expertise required for these expensive therapies.[4]

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase 5. This isoenzyme metabolizes cGMP which is the second messenger of NO and a principle mediator of smooth muscle relaxation and vasodilatation. By inhibiting the hydrolytic breakdown of cGMP, sildenafil prolongs the action of cGMP. This results in augmented smooth muscle relaxation and causes pulmonary vasodilatation. Sildenafil decreases pulmonary vascular resistance in pulmonary hypertensive neonate.[5,6]

Oxygenation indices:[7]

1. OI: Mean airway pressure (MAP)×FiO2/PaO_2×100
   Reference ranges:
   <3 - Normal
   5 to 10 - Need supplemental oxygen
   >12 - FiO_2 0.4 with continuous positive airway pressure (CPAP) 4 cm H_2O
   >15 - Ventilator care with FiO_2<0.6
   >20 - Ventilator care with FiO_2>0.6
   >25 - HFOV with NO
   >40 - ECMO
2. $AaDO_2$ (Alveolar-Arterial gradient)=PAO_2-PaO_2
   PAO_2 = (Atmospheric barometric pressure – water vapor pressure) × FiO_2- $PaCO_2$
   Atmospheric barometric pressure = 680 in Bengaluru
   Values interface:
   100 - Normal
   100 to 200 - Mild degree of gas exchange defect
   >250 - Moderate degree of gas exchange defect (needs ventilation)
   >400 - Severe degree of gas exchange defect with shunting
   >600 - ECMO
3. a/A ratio
   Normal values: 0.7-0.9
   <0.3 severe respiratory impairment
   <0.2 need for surfactant or Severe PPHN
4. SOPI = Saturation oxygen distending pressure index (for non-invasive ventilation)
   SOPI=PEEP × FIO_2/SPO_2
   <2 – Mild pulmonary dysfunction (OI – <5)
   2 to 3 – Moderate pulmonary dysfunction (OI – 5 to 15)
   >3 – Severe pulmonary dysfunction (OI – >15).

MATERIALS AND METHODS

This is a prospective observational case study conducted during January 2008 to January 2016 on babies admitted in our neonatal intensive care unit of Vydehi Institute of Medical Sciences with PPHN on invasive or non-invasive ventilation (resource-limited setting).

All the babies admitted to neonatal intensive care unit are screened for PPHN by echocardiography (ECHO). All babies with pulmonary artery pressures (PAP) on ECHO >25 mm of Hg with a gestation of more than 34 weeks and OI >20 are included in the study. If associated with Hyaline membrane disease diagnosed by clinical features and X-ray findings or having any congenital heart diseases are excluded from the study.

OI, oxygen saturations (SpO_2), alveolar-arterial oxygen gradient (A-aDO_2), a/A ratio, and SOPI (for non-invasive ventilated babies) were monitored serially every 6 h. ECHO is done before and every 6th hourly after starting sildenafil to assess the PAP. All the babies, invasive or non-invasive ventilated, are evaluated for all the parameters separately.

Table 1: Demographic details of babies with PPHN

Causes	M/F	Inborn/ out born	Term/ preterm	Ventilated/CPAP with sildenafil	Death
Group 1. Persistent pulmonary vasoconstriction					
Asphyxia (*n*=35)	21/14	24/11	28/7	31/4	5
MAS (*n*=83)	54/29	61/22	81/2	71/12	11
RDS (*n*=192)*	98/94	102/90	0/192	NI	NI
Sepsis/pneumonia (*n*=30)	15/16	23/07	23/7	25/5	4
Idiopathic (*n*=11)	6/5	8/3	9/2	11/0	2
Group 2. Functional vascular bed obstruction of pulmonary vessels					
Polycythemia (*n*=3)	1/2	2/1	1/2	3/0	0
Group 3. Decreased pulmonary vascular bed					
CDH (*n*=10)	7/3	7/3	8/2	10/0	4
Oligohydraminos with pulmonary hypoplasia (*n*=15)	8/7	9/6	13/2	15/0	5
Pleural effusion with pulmonary hypoplasia (*n*=2)	2/0	2/0	2/0	2/0	1
Group 4. Pulmonary venous hypertension*					
TAPVC (*n*=7)	5/2	3/4	5/2	NI	NI
HLH (*n*=6)	4/2	5/1	5/1	NI	NI
Obstruction of left ventricular outflow (*n*=2)	2/0	2/0	2/0	NI	NI
Total (*n*=397)	223/174	246/147	167/219	168/21	32

NI: Not included, *Not included in the study, MAS: Meconium aspiration syndrome, CDH: Congenital diaphragmatic hernia, CPAP: Continuous positive airway pressure, TAPVC: Total anomalous pulmonary venous connection

Table 2: Sildenafil and its effect on oxygenation indices in non-invasive ventilated babies

Causes	Time	PaO_2	$A\text{-}aDO_2$ (mm of hg)	a/A ratio	SOPI	ECHO-PA pressures		*P* value
						Before sildenafil	After sildenafil	
Asphyxia (*n*=4)	0	52±3	194±25	0.52±0.4	3.4±0.2	68±7	68±7	<0.01
	1	53±4	190±18	0.53±0.4	3.2±0.3		67±7	
	2	56±6	185±25	0.56±0.4	2.7±0.2		67±5	
	6	58±5	180±25	0.59±0.4	2.5±0.3		63±5	
	12	62±4	172±25	0.60±0.4	2.2±0.2		58±6	
	18	62±6	160±25	0.62±0.4	2.2±0.2		53±5	
	24	65±5	151±25	0.64±0.4	1.9±0.3		51±6	
	30	65±5	147±25	0.64±0.4	1.6±0.2		48±7	
	36	67±4	138±25	0.68±0.4	1.5±0.2		35±5	
	42	69±3	125±25	0.72±0.4	1.5±0.2		32±4	
	48	71±3	105±25	0.74±0.4	1.5±0.3		32±4	
	72	71±4	63±25	0.78±0.4	1.5±0.2		22±5	
MAS (*n*=12)	0	45±5	203±25	0.44±0.4	3.6±0.2	76±5	76±7	<0.01
	1	45±3	201±25	0.46±0.4	3.7±0.2		74±8	
	2	46±4	197±25	0.48±0.4	2.8±0.3		74±5	
	6	48±2	178±25	0.51±0.4	2.8±0.2		68±6	
	12	51±4	164±25	0.52±0.4	2.4±0.1		63±7	
	18	54±4	143±25	0.54±0.4	2.2±0.3		58±7	
	24	57±4	124±25	0.58±0.4	2.1±0.2		53±5	
	30	59±3	112±25	0.60±0.4	2.1±0.2		44±6	
	36	59±2	108±25	0.62±0.4	2.0±0.1		39±6	
	42	61±5	89±25	0.64±0.4	1.6±0.2		31±4	
	48	62±4	77±25	0.70±0.4	1.6±0.3		27±4	
	72	64±3	64±25	0.74±0.4	1.6±0.2		21±2	
Sepsis/pneumonia (*n*=5)	0	51±4	186±25	0.58±0.4	3.1±0.2	77±6	77±6	<0.01
	1	51±3	184±25	0.58±0.4	3.1±0.2		76±5	
	2	51±3	175±25	0.59±0.4	2.8±0.3		76±6	
	6	52±4	165±25	0.64±0.4	2.6±0.2		74±5	
	12	55±3	154±25	0.67±0.4	2.6±0.3		67±5	
	18	56±2	143±25	0.71±0.4	2.2±0.2		62±4	
	24	58±5	136±25	0.71±0.4	2.1±0.3		59±4	
	30	62±3	125±25	0.75±0.4	2.1±0.2		46±5	
	36	64±2	121±25	0.75±0.4	1.9±0.2		35±3	
	42	65±3	107±25	0.76±0.4	1.6±0.3		32±4	
	48	67±3	98±25	0.77±0.4	1.6±0.2		27±5	
	72	71±3	79±25	0.81±0.4	1.4±0.1		19±4	

MAS: Meconium aspiration syndrome, CDH: Congenital diaphragmatic hernia, ECHO: Echocardiography, SODPI: Saturation oxygen distending pressure index

Table 3: Sildenafil and its effect on oxygenation indices in invasive ventilated babies

Causes (*n*=167)	Time	PaO_2	A-aDO_2	a/A ratio	OI	ECHO-PA pressures		*P* value
						Before sildenafil	After sildenafil	
Group 1. Persistent pulmonary vasoconstriction								
Asphyxia (*n*=29)	0	54±6	384±16	0.47±0.4	46±3	68±7	68±7	<0.01
	1	54±6	377±15	0.47±0.4	46±3		67±7	
	2	54±6	363±14	0.48±0.4	45±3		67±5	
	6	54±6	341±19	0.49±0.4	44±3		63±5	
	12	54±6	282±22	0.51±0.4	43±3		58±6	
	18	54±6	263±17	0.54±0.4	42±3		53±5	
	24	54±6	259±16	0.55±0.4	41±3		51±6	
	30	54±6	221±18	0.57±0.4	36±3		48±7	
	36	54±6	211±13	0.59±0.4	33±3		35±5	
	42	54±6	187±14	0.61±0.4	31±3		32±4	
	48	76±6	145±13	0.66±0.4	29±3		32±4	
	72	81±6	123±9	0.72±0.4	24±3		22±5	
MAS (*n*=73)	0	54±6	441±20	0.42±0.4	49±3	76±7	76±7	<0.01
	1	54±6	407±14	0.42±0.4	48±3		74±8	
	2	54±6	396±14	0.44±0.4	45±3		74±5	
	6	54±6	385±16	0.46±0.4	42±3		68±6	
	12	54±6	367±14	0.48±0.4	38±3		63±7	
	18	54±6	325±15	0.51±0.4	35±3		58±7	
	24	54±6	301±21	0.54±0.4	31±3		53±5	
	30	54±6	287±22	0.57±0.4	29±3		44±6	
	36	54±6	243±18	0.59±0.4	24±3		39±6	
	42	54±6	204±13	0.63±0.4	23±3		31±4	
	48	54±6	187±15	0.64±0.4	23±3		27±4	
	72	54±6	165±21	0.69±0.4	21±3		21±2	
Sepsis/pneumonia (*n*=25)	0	54±6	320±21	0.51±0.4	44±3	77±6	77±6	<0.01
	1	54±6	318±23	0.54±0.4	42±3		76±5	
	2	54±6	289±15	0.56±0.4	39±3		76±6	
	6	54±6	256±17	0.57±0.4	35±3		74±5	
	12	54±6	234±15	0.57±0.4	32±3		67±5	
	18	54±6	202±18	0.59±0.4	31±3		62±4	
	24	54±6	187±17	0.61±0.4	28±3		59±4	
	30	54±6	164±15	0.63±0.4	27±3		46±5	
	36	54±6	154±21	0.64±0.4	24±3		35±3	
	42	54±6	113±17	0.65±0.4	22±3		32±4	
	48	54±6	103±13	0.68±0.4	22±3		27±5	
	72	54±6	89±12	0.74±0.4	20±1		19±4	
Idiopathic (*n*=11)	0	54±6	388±25	0.54±0.4	49±3	68±7	68±7	<.01
	1	54±6	372±25	0.54±0.4	47±3		67±7	
	2	54±6	354±25	0.54±0.4	44±3		67±5	
	6	54±6	321±25	0.54±0.4	43±3		63±5	
	12	54±6	302±25	0.54±0.4	40±3		58±6	
	18	54±6	288±25	0.54±0.4	39±3		53±5	
	24	54±6	264±25	0.54±0.4	37±3		51±6	
	30	54±6	224±25	0.54±0.4	36±3		48±7	
	36	54±6	187±25	0.54±0.4	34±3		35±5	
	42	54±6	165±25	0.54±0.4	32±3		32±4	
	48	54±6	143±25	0.54±0.4	32±3		32±4	
	72	54±6	112±25	0.54±0.4	32±3		22±5	
Group 2. Functional vascular bed obstruction of pulmonary vessels								
Polycythemia (*n*=43)	0	52±3	272±25	0.54±0.4	38±3	74±8	74±8	<0.01
	1	53±4	265±25	0.54±0.4	37±3		74±5	
	2	56±6	254±25	0.54±0.4	35±3		68±6	
	6	58±5	233±25	0.54±0.4	35±3		63±7	
	12	62±4	207±25	0.54±0.4	33±3		58±7	
	18	62±6	189±25	0.54±0.4	32±3		53±5	
	24	65±5	154±25	0.54±0.4	30±3		44±6	
	30	65±5	143±25	0.54±0.4	29±3		39±6	
	36	67±4	132±25	0.54±0.4	27±3		31±4	
	42	69±3	121±25	0.54±0.4	24±3		27±4	

(Contd...)

Table 3: (*Continued*)

Causes (*n*=167)	Time	PaO_2	A-aDO_2	a/A ratio	OI	ECHO-PA pressures		*P* value
						Before sildenafil	After sildenafil	
	48	71±3	101±25	0.54±0.4	24±3		21±2	
	72	71±4	88±25	0.54±0.4	23±3		19±6	
Group 3. Decreased pulmonary vascular bed								
CDH (*n*=10)	0	45±3	394±25	0.54±0.4	46±3	76±6	76±6	<0.01
	1	46±4	380±25	0.54±0.4	45±3		74±5	
	2	48±2	376±25	0.54±0.4	45±3		67±5	
	6	51±4	356±25	0.54±0.4	43±3		62±4	
	12	54±4	334±25	0.54±0.4	41±3		59±4	
	18	57±4	311±25	0.54±O.4	39±3		46±5	
	24	59±3	287±25	0.54±0.4	39±3		35±3	
	30	59±2	265±25	0.54±0.4	36±3		32±4	
	36	61±5	231±25	0.54±0.4	35±3		27±5	
	42	62±4	219±25	0.54±0.4	32±3		29±4	
	48	63±3	187±25	0.54±0.4	29±3		32±2	
	72	65±4	154±25	0.54±0.4	28±3		31±3	
Oligohydraminos with pulmonary hypoplasia (*n*=15)	0	51±3	431±25	0.41±0.4	46±3	78±7	78±7	<0.01
	1	51±3	426±25	0.43±0.4	46±3		77±7	
	2	52±4	423±25	0.44±0.4	44±3		75±5	
	6	55±3	411±25	0.45±0.4	45±3		73±5	
	12	56±2	387±25	0.47±0.4	42±3		68±6	
	18	58±5	365±25	0.51±0.4	41±3		63±5	
	24	62±3	354±25	0.54±0.4	39±3		61±6	
	30	64±2	321±25	0.57±0.4	37±3		54±7	
	36	65±3	302±25	0.58±0.4	38±3		45±5	
	42	67±2	287±25	0.58±0.4	33±3		38±4	
	48	71±3	223±25	0.63±0.4	32±3		34±4	
	72	73±2	191±25	0.67±0.4	30±3		32±5	
Pleural effusion with pulmonary hypoplasia (*n*=2)	0	52±3	378±25	0.39±0.4	31±3	76±7	76±7	<0.01
	1	53±4	360±25	0.39±0.4	31±3		74±8	
	2	56±6	354±25	0.40±0.4	32±3		74±5	
	6	58±5	343±25	0.44±0.4	30±3		68±6	
	12	62±4	323±25	0.44±0.4	28±3		63±7	
	18	62±6	311±25	0.46±0.4	27±3		58±7	
	24	65±5	290±25	0.47±0.4	27±3		53±5	
	30	65±5	268±25	0.49±0.4	25±3		44±6	
	36	65±4	223±25	0.52±0.4	25±3		39±6	
	42	67±3	187±25	0.58±0.4	25±3		31±4	
	48	69	143	0.57	24		27	
	72	69	138	0.64	24		21	

ECHO: Echocardiography, MAS: Meconium aspiration syndrome, CDH: Congenital diaphragmatic hernia

Sildenafil tablet (50 mg) is 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. Babies are considered responsive to therapy if at least 2 out of the three indicators are present from the baseline values:

- SaO2 >10% increase in ABG
- OI decreases by 10-20%
- Decrease in FiO2 by 5-10%.

The main outcome variable was the effect of oral sildenafil on oxygenation indices. Sildenafil was discontinued when OI was <15 or hypotension in spite of the baby on inotropes or if there was no significant change in OI after 8 doses (non-responsive).

Statistical Analysis

Data analysis was performed using the SPSS software (version 16; SPSS 2007, Chicago, Illinois, USA). Categorical variables are presented as percentages and numbers. Continuous variables were presented as means (standard deviation) in normally distributed variables. Comparisons between categorical variables were performed using χ^2 test (independent variables), assessed in mortality, sex, ventilated or CPAP and gestational age. Depending on the type of variable, a Mann-Whitney *U* test, a Kruskal–Wallis

test, a Spearman's rank correlation coefficient, and a *T*-test, one-way analysis of variance were used. In these tests, a $P < 0.01$ was considered significant.

RESULTS

In our study, a total of 397 babies had PPHN of which 207 babies were excluded as they had hyaline membrane disease and congenital heart disease. Out of 187 included in the study, 167 had invasive ventilation and remaining was on CPAP. 32 babies included in the study died during or after the study period of various causes related to the disease process (Table 1).

Out of 22 babies on CPAP with PPHN, 18% had birth asphyxia, 54% had MAS, and remaining had sepsis/pneumonia. All the babies had a significant decrease in PA pressures on all babies on non-invasive ventilation for different causes over 3 days of the treatment with oral sildenafil. There was also significant decrease in PaO_2, A-aDO_2a/A ratio and SOPI (Table 2).

About 168 (89%) babies with PPHN were on ventilator, of which 19% of the babies died of various reasons. No adverse effects like severe hypotension or pulmonary hemorrhage were noticed due sildenafil. In Group 1 cases with severe persistent vasoconstriction (asphyxia, MAS, sepsis/pneumonia or idiopathic), there was a significant decrease in PA pressures by 72 h. In polycythemia babies with PPHN on ventilator all babies survived and there was significant decrease in PA pressures from (Table 3).

DISCUSSION

PPHN is a serious neonatal emergency, which contributes to neonatal hypoxemia that is often refractory and is associated with a high mortality. The most effective types of the treatment of PPHN including inhaled NO (iNO) and ECMO are not available in many of the developing countries, hence search for other options like oral sildenafil was tried. We used sildenafil at a starting dose of 0.5 mg/kg/day and increased if no response as per the criteria. The dose was increased in 64 (33%) of the cases included in the study. There was no response in 12 cases even with a maximum dose of 2mg/kg of sildenafil.

A Cochrane review on sildenafil for pulmonary hypertension in neonates included two randomized controlled trials conducted in resource-limited settings where iNO and high-frequency oscillatory ventilation (HFOV) are not available. Both included neonates in need of mechanical ventilation (with OI ≥25) and echocardiographically confirmed PPHN. In our study, a resourced limited without availability of iNo and HFOV; there was statistically significant improvement in the PAP in ECHO and OI.[8]

Baquero *et al.* compared oral sildenafil with placebo and evaluated its effect on oxygenation in PPHN in 13 neonates ≥35.5 weeks' gestation with severe hypoxemia. Neonates in the treatment group were found to have improved OI and SpO2 and a markedly lower mortality rate. In our study babies on invasive ventilation, there is an improvement in the OI, PaO_2, A-aDO_2, a/A ratio and PA pressures by ECHO.[9]

Herrera *et al.* compared conventional management of newborn infants with PPHN with and without the addition of sildenafil (sildenafil 13 cases, placebo 11) and showed significant improvement in OI in the treatment group. In addition, the pressure arterial oxygen (PaO_2) at 72 h was better and MAP and number of ventilation days lower in the sildenafil group. In our study, there was a significant decrease in PPHN in babies on invasive ventilation with birth asphyxia, MAS and Sepsis/pneumonia group within 72 h and sildenafil was stopped in view of decrease in PA pressures and OI. Whereas in babies with PPHN due to idiopathic, CDH or pulmonary hypoplasia causes the drug was continued for more than 72 h and few cases who survived and discharged with sildenafil and were followed up.[10]

Adverse effects of sildenafil include gastrointestinal, cardiovascular, visual, auditory, central nervous system, and possibly hemostatic disturbances. In our study, no significant side effects were observed requiring the drug to be stopped.

CONCLUSION

Sildenafil given orally was well tolerated with no adverse events documented during the treatment. Improved oxygenation was demonstrated by an increase in the PaO_2, decrease in PA pressures, improvement in OI, and ability to manage of PPHN with conventional methods in a resource-limited set up. To conclude, oral sildenafil (0.5 mg/kg/dose/12 h) may be a safe and effective treatment for PPHN in non-ventilated and ventilated neonates of different etiologies.

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