CASE SERIES

ORAL SILDENAFIL USE IN NEONATES WITH PERSISTENT PULMONARY HYPERTENSION OF NEWBORN

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Background: The prevalence of PPHN has been estimated at 1.9 per 1000 live births. After the discovery of iNO's, its efficacy and benefit in PPHN is well established. Even in the best of centers equipped with iNo and ECMO the mortality is around 20%. Also, iNO is expensive and difficult to administer and monitor which makes it difficult choice in our part of the world. Furthermore About 40% of patients do not respond or have rebound pulmonary hypertension after discontinuation. Owing to these reasons, other treatment modalities like phosphodiesterase inhibitors such as Sildenafil need to be evaluated. **Methods**: We report a retrospective case series of eighteen patients with PPHN admitted in NICU and treated with oral sildenafil. **Results**: Three (17%) babies had mild, 5 (28%) moderate and 10 (55%) severe PPHN based on echocardiography. Sildenafil was started on all patients on a mean of 1.67 days and stopped on mean 12.6 days. Initial fio2 was 100%, which after starting sildenafil decreased gradually to 40% on mean 10 days. Average length of stay in NICU was 13 days. Twelve (67%) patients survived whereas 6 (33%) expired (Figure 2). No improvement in oxygen Index after 36 hours (p<0.05) was the independent predicting risk factor for PPHN related mortality in the expired patients. **Conclusion**: Oral sildenafil can be a used in conjunction with other treatment modalities for PPHN especially in resource limited settings. However further studies regarding its comparative efficacy need to be done.

Keywords: PPHN; Sildenafil; Neonate; Pulmonary hypertension; Management; Neonatal ICU
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INTRODUCTION

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a condition characterized by increased pulmonary vascular resistance, extra pulmonary shunting of blood from right to left through patent circulatory channels (including foramen ovale and ductus arteriosus), and consequently, hypo-perfusion of lungs.[1] The prevalence of PPHN has been estimated at 1.9 per 1000 live births.[1] Physiologically, there is maladaptation of the lungs to the extra-uterine condition and inadequate transition from fetal to neonatal circulation causing abnormal tone and reactivity of pulmonary vasculature leading to sustained pulmonary hypertension.[2] PPHN can result in serious morbidity and can be potentially fatal. Even in the best of centers equipped with iNo and ECMO the mortality is 20%.[3] We report a case series of eighteen patients with PPHN admitted in NICU and treated with sildenafil for echocardiogram (ECHO) diagnosed PPHN due to unavailability of inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO).

Persistent Pulmonary Hypertension of Newborn (PPHN) is found in about 0.34–6.8 per 1000 live births and mortality occurs in 10–20% of the cases.[4] iNO is considered the mainstay of treatment but it is often unavailable in resource limited areas. Literature also suggests that iNO is sometimes seen to cause rebound pulmonary hypertension upon discontinuation.[4] Furthermore, long term use of iNO is not feasible because of its short half-life.[5,6] Inhaled nitric oxide is expensive and difficult to administer and monitor.[5] Moreover, studies show that about 40% of the patients may not respond to iNO fully and these patients may require additional treatment such as ECMO.[5] Also, it is known that at oxygenation index (OI) >25, iNO decreases the use of ECMO, but does not alter the overall mortality.[6] Owing to these reasons, other treatment options such as Vasodilators; Prostacyclin (PGE1), Nitric oxide precursors like L-arginine, Free radical scavengers and Phosphodieterase inhibitors such as Sildenafil need to be explored for efficacy and safety.

MATERIAL AND METHODS

Retrospective review of medical records of all neonates admitted in our neonatal intensive care unit (NICU) with the diagnosis of PPHN who received sildenafil was done after approval from ERC (2743-Ped-ERC-13). PPHN was suspected based on the difference in pre-post ductal oxygen saturations of more than 15%, persistent hypoxia defined as Pao2 <50 mmHg, and oxygen requirement of 100% oxygen on admission. Severity of PPHN on ECHO was determined by direction of shunt at ductus arteriosus and foramen ovale and tricuspid regurgitation flow velocity. All Patients with underlying congenital heart disease and lung hypoplasia were excluded. All neonates who had sepsis, evident from positive blood cultures, were also excluded. Sildenafil was administered to all neonates in oral form with dose of 2 mg/kg/dose three times a day. Sildinafil was continued until

extubation. OI was calculated at baseline with formula:

$$OI = \frac{F_iO_2 \times MAP}{P_aO_2}$$

Treatment was supplemented with antibiotics, analgesia, sedation, and inotropes and suctioning. All babies were kept on a minimal-handling status. Variables that were recorded include demographic and anthropometric data. Other Data include Apgar score at 5 minutes, Meconium stained liquor, clinical symptoms, maternal comorbid, average length of stay, mortality, need for ventilation along with vent settings and chest radiographs. Dose and duration of sildinafil were also recorded (Table 1). Outcome was assessed by the difference in Fio2 requirement after starting sildenafil, time taken to get off the ventilator and mortality. Secondary out comes were assessed by univariate and multivariate analysis.

RESULTS

Total of 18 neonates were enrolled out of which fourteen were male and four were female. Thirteen patients were term (>37 weeks gestation) and five near term (35–37 weeks gestation). Four mothers had pregnancy induced hypertension (PIH) whereas; one mother was diagnosed with gestational diabetes and one with urinary tract infection (UTI). Five patients were delivered via normal vaginal delivery whereas; ten via emergency cesarean section and three via elective cesarean section. Eleven out of eighteen patients had good APGAR scores at birth. From those who did not have good apgar scores, five required immediate resuscitation with positive pressure ventilation. Eight babies had meconium stained amniotic fluid out of which five were suspected to have meconium aspiration. All patients required some inotropic support in the form of Dopamine (n: 15, 83%), dobutamine (n: 10, 55%) and epinephrine (n: 4; 22%).

Based on echocardiography; 3 (17%) patients had mild, 5 (28%) moderate and 10 (55%) severe PPHN. Whereas X-ray was reported to be RDS in 5 (28%) cases. Mean oxygen index (OI) was 44.32 on admission. Sildenafil was started on all patients on a mean of 1.67 days and stopped on mean 12.6 days. Mean starting dose was 5.4 mg/day. Initial fio2 was 100%, which after starting sildenafil decreased gradually to 40% on mean 10 days (Figure 1). Average length of stay in NICU was 13 days. Twelve (67%) patients survived whereas 6 (33%) expired (Figure 2). No improvement in oxygen Index after 36 hours ($p<0.05$) was the independent predicting risk factor for PPHN related mortality in the expired patients.

DISCUSSION

PPHN is a disease with serious outcomes. The patients are often critically ill and need immediate ventilation. The pathophysiology of PPHN can be divided into three broad categories- increased pulmonary vasoconstriction, abnormal pulmonary vascular development, and decreased pulmonary vascular bed (lung hypoplasia).[5] Causes that lead to these changes are not fully understood but perinatal hypoxia, meconium aspiration, acidosis, hypothermia and structural lung malformations such as diaphragmatic hernia and maternal use of non-steroidal anti-inflammatory drugs in the third trimester of pregnancy are all associated with increased risk of PPHN.[5]

Clinical diagnosis of PPHN is made on the basis of hypoxemia refractory to oxygen therapy.[4] Right to left shunting is confirmed with the pre- and post-ductal oxygen saturation levels.[4] Chest radiography is used to diagnose the presence of underlying lung pathologies such as pneumonia and meconium aspiration syndrome. Echocardiography is done to confirm the diagnosis with findings of elevated Tricuspid Regurgitation (TR) pressures. Echocardiography is also done to rule out any congenital cardiac anomaly.[6]

Several management options are available worldwide, including iNO and ECMO.[6] Developing countries often have problems accessing these facilities. In such settings, Sildenafil, a specific Phosphodiesterase 5 (PDE-5) inhibitor, even when used as a monotherapy, seems to be a good treatment option. Despite the fact that we have limited knowledge of Sildenafil safety and use, we continue to use it because of the limited choices neonatologists have for the treatment of PPHN.[7]

Sildenafil is a type 5 Phosphodiesterase (PDE) inhibitor. Like iNO, Sildenafil is a vasodilator specific for pulmonary vasculature.[7,8] By inhibiting PDE, sildenafil increases the intracellular cAMP and cGMP levels, leading to vascular smooth muscle relaxation in the pulmonary vascular bed.[8] Studies have shown that Sildenafil can be used successfully to improve the oxygenation parameters in neonates with PPHN.[9]

Shah and Ohlsson; in cochrane data base (2011) reviewed three RCTs looking at the efficacy of sildenafil and concluded that there was significant reduction in mortality in sildenafil group. Therefore, Sildinafil has significant potential especially in resource limiting settings. However, whether sildenafil can completely replace iNO as the gold standard of treatment for PPHN is still unknown.[10]

Baquero *et al* showed that oral sildenafil improved Oxygenation Index in critically sick patients with severe degree of PPHN.[11] The study however concluded that they could not say whether sildenafil increased survival in these patients.[11] In our study, infants admitted with PPHN responded to oral sildenafil therapy as evident by decrease in the fractional inspiratory Oxygen demand in these patients over a period of ten days. We acknowledge that following the

FiO2 may not present a very accurate picture of the oxygenation dependence. In our study, we did not look for any adverse outcomes of the drug.

The treatment of PPHN is mainly supportive and since the underlying pathology involves hypoxemia due to elevated pulmonary vascular resistance, selective pulmonary vasodilatation is the aim of medical management of PPHN.[12,13] Meconium aspiration syndrome is one of the most important causes of morbidity and mortality in babies with PPHN as discussed by Shekerdemian *et al*.[14] However, our study showed that meconium aspiration syndrome was present in only five patients out of whom two developed severe PPHN and three moderate PPHN. Our study reported that respiratory distress syndrome is also a most common symptom of PPHN.

Table-1: Patients characteristics and outcomes

	n (%)
Gender	
Female	4 (78)
male	14 (22)
Gestation	
Term > 37 wks	13 (72)
Near term 35-37 wks	5 (28)
Mode of delivery:	
SVD	5 (27)
Emergency Cesarean section	10 (56)
Elective Cesarean section	3 (17)
Apgar at 5 minutes:	
good	11 (61)
poor	7 (39)
Immediate resuscitation:	
Dry and stimulate	8 (44)
PPV	5 (28)
Intubation and MV	5 (28)
Meconium stained Liquor	8 (44)
Meconium Aspiration syndrome	5 (28)
Clinical Features	
Cyanosis	3 (17)
Apnea	1 (5)
Hypothermia/hyperthermia	0 (0)
Grunting	10 (55)
Tachypnea	12 (67)
Signs of respiratory distress	14 (78)
Bradycardia	3 (17)
Maternal comorbid	
Pregnancy induced Hypertension	4 (22)
Gestational Diabetes	1 (5)
Urinary tract infection	1 (5)
None	14 (78)
Associated conditions, number:	
Respiratory distress syndrome	5 (28)
Meconium aspiration Syndrome	5 (28)
Pneumonia	1 (5.6)
NEC	0 (0)
IVH	0 (0)
inotropic Support	15 (83)
Dopamine	15 (83.3)
Dobutamine	10 (55)
Adrenaline	4 (22)
Average Length of stay (days)	12.4
Outcome	
Survived	12 (67)
Expired	6 (33)
	n (%)
Severity of PPHN based on echo	
Mild	3 (17)
Moderate	5 (28)
Severe	10 (55)
Ventilator Mode:	
SIMV	11 (61)
CMV	2 (11)
HFO	5 (27)
Mean oxygenation index on admission	44.32
Mean Airway Pressure	18
Chest Radiograph:	
Normal	3 (16)
RDS	9 (50)
Pulmonary Edema	1 (5.6)
PIE	1 (5.6)
MAS	1 (5.6)
Pneumothorax	1 (5.6)
Atelactasis	1 (5.6)
Image not available	1 (5.6)
Sildenafil	
started at day of life (Mean)	1.67
Stopped at day of life (Mean)	12.6
Dose (mean dose in mg/kg/day)	5
Initial Fio2 when sildenafil started	0.1
Mean duration of mechanical ventilation in days	10
Average length of stay in NICU in days	13

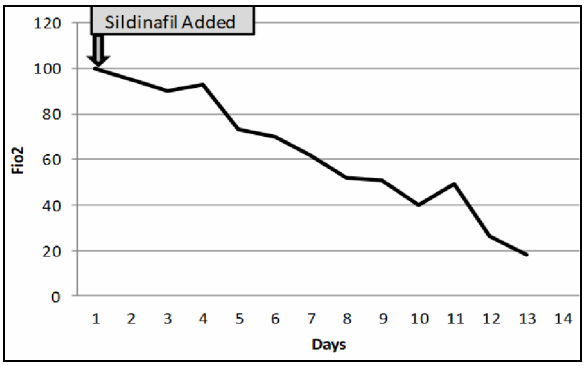

Figure-1: Decrease in oxygen requirement in days following sildenafil administration

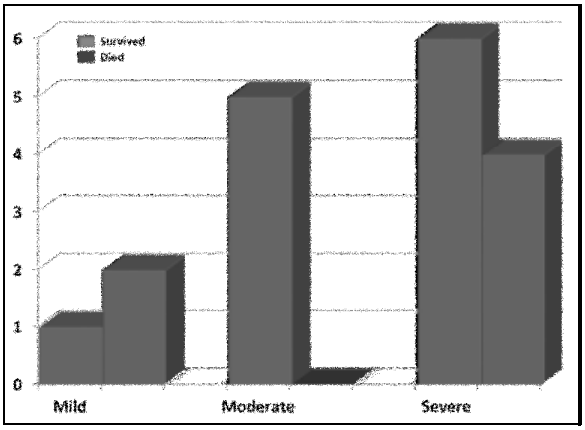

Figure-2: Outcomes according to the severity of PPHN based on ECHO

CONCLUSION

Current literature suggests good evidence of the use of sildenafil in PPHN[8]. The findings of this study suggest that oral sildenafil can be successfully used to improve oxygenation in patients with PPHN especially in a resource-limited setting where facilities like ECMO and inhaled nitric oxide are not available. With sildenafil effectively lowering the oxygen requirement and probably improving the mortality rate in these patients, there is a possibility of concluding the need for the more sophisticated modalities. However, these findings cannot be generalized because small sample size. We also acknowledge that our study could not adequately rule out the possibility of side effects associated with sildenafil use. COI statement: The authors have no conflicts of interest relevant to this article.

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