

Case Report

Role of oral sildenafil in neonates with persistent pulmonary hypertension of newborn

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ABSTRACT

Persistent pulmonary hypertension of newborn is a devastating condition and leads to morbidity and mortality. Even after the increasing use of NO, ECMO and HFO many patients succumb to death. About 50% of the patients either have rebound hypertension or do not respond to the treatment. Hence the role of phosphodiesterase inhibitors (sildenafil) need to be evaluated. Methods is authors report a retrospective case series of 24 patients with PPHN admitted in NICU and treated with oral sildenafil. Results sildenafil was started on all patients on a mean of 1.46 days and stopped on mean of 3.8 days. Initial fio₂ was 100%, which after starting sildenafil decreased gradually to 50% on mean of 10 days. Average length of stay in NICU was 20 days. 17(70.8%) patients survived whereas 7 (29%) expired. No improvement in oxygen Index after 48 hours ($p < 0.05$) was the independent predicting risk factor for PPHN related mortality in the expired patients. Conclusion are oral sildenafil can be a used in conjunction with other treatment modalities for PPHN especially in resource limited settings.

Keywords: Neonate, Persistent pulmonary hypertension of the newborn, phosphodiesterase inhibitors, Persistent pulmonary hypertension, Sildenafil, Neonatal intensive care unit

INTRODUCTION

Physiologically, there is inadequate transition from fetal to neonatal circulation causing increased pulmonary vasculature leading to sustained pulmonary hypertension.¹ Persistent Pulmonary Hypertension of the Newborn (PPHN) is a condition characterized by increased pulmonary vascular resistance leading to shunting of blood from right to left through patent circulatory channels (including foramen oval and ductus arteriosus), and consequently, hypo-perfusion of lungs.² PPHN can result in serious morbidity and can be potentially fatal.

Even in the centers equipped with in and ECMO the mortality is 20%.³ Authors report a case series of 28

patients with PPHN admitted in NICU and treated with sildenafil for PPHN diagnosed on clinical grounds due to unavailability of inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO). Long term use of iNO is not feasible because of its short half-life and it is expensive and difficult to administer.⁴ Studies show that about 40% of the patients may not respond to iNO fully and these patients may require additional treatment such as ECMO.⁴ iNO is considered the mainstay of treatment but it is often unavailable in resource limited areas. iNO is sometimes seen to cause rebound pulmonary hypertension upon discontinuation.⁵ At oxygenation index (OI) >25, iNO decreases the use of ECMO, but does not alter the overall mortality. Thus Phosphodiesterase inhibitors such as Sildenafil need to be evaluated for efficacy and safety.

CASE REPORT

Retrospective review of medical records of all 28 neonates admitted in our neonatal intensive care unit (NICU) during a span of 6 months with the diagnosis of PPHN who received sildenafil was done after approval from ethical committee. PPHN was suspected based on the difference in pre-post ductal oxygen saturations of more than 15% and hypoxia defined as $Pao_2 < 50\text{mmHg}$ and FiO_2 need of 100%. Patients with underlying congenital heart disease 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 1 mg/kg/dose four times a day and was continued until extubation. OI was calculated at baseline with formula: $FiO_2 \times MAP / PaO_2$. Antibiotics, sedation and inotropes were also given according to the clinical condition. Variables that were recorded includes demographic data, Apgar score, Meconium stained liquor, symptoms, maternal comorbidity, length of stay, outcome, need for ventilation along with venti settings and chest radiographs.

Dose and duration of sildenafil were also recorded. Outcome was assessed by the difference in FiO_2 requirement after starting sildenafil, time taken till extubation and mortality. Secondary outcomes were assessed by univariate and multivariate analysis.

RESULTS

Total of 24 neonates were enrolled and all were of term gestation. None of the mothers had any comorbidity. 19 patients were delivered via normal vaginal delivery whereas 5 by cesarean section. 20 out of 24 patients had poor APGAR scores at birth and required immediate resuscitation with positive pressure ventilation. 20(83.3%) babies had meconium stained amniotic fluid and were suspected to have meconium aspiration. All patients required some inotropic support in the form of Dopamine (n: 15, 62.5%), dobutamine (n: 20, 83.3%) and epinephrine (n: 8; 33.3%) and all of them required mechanical ventilation. 18(75%) babies received High Frequency Ventilation and 6(25%) received SIMV. X-Rays of the babies with meconium aspiration (20, 83.3%) showed whiteout lungs with atelectasis while the rest had clear lung fields.

The cardiac shadow was essentially normal. Mean oxygen index (OI) was 40.32 on admission. Sildenafil was started on all patients on a mean of 1.46 days and stopped on mean 3.8 days. Starting dose was 1mg/kg/dz. Initial FiO_2 was 100%, which after starting sildenafil decreased gradually to 50% on mean of 10 days. Average length of stay in NICU was 20 days. 17(70.8%) patients survived whereas 7 (29%) expired. No improvement in oxygen Index after 48 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 often need immediate ventilation. The pathophysiology is increased pulmonary vasoconstriction, abnormal pulmonary vascular development, and decreased pulmonary vascular bed.⁴ Echocardiography confirms the diagnosis with findings of elevated Tricuspid Regurgitation (TR) pressures and rules out any congenital cardiac anomaly.⁶ Causes may be perinatal hypoxia, meconium aspiration, acidosis or structural lung malformations such as diaphragmatic hernia.⁴ Clinical diagnosis of PPHN is made on the basis of hypoxemia refractory to oxygen therapy and with the difference in pre- and postductal oxygen saturation.⁵ Chest radiography is used to diagnose the presence of underlying lung pathologies. Management options are iNO, ECMO. Developing countries often have problems accessing these facilities. Sildenafil, a specific Phosphodiesterase 5 (PDE-5) inhibitor, even when used as a monotherapy, seems to be a good treatment option. Like iNO, Sildenafil is a vasodilator specific for pulmonary vasculature and by inhibiting PDE, sildenafil increases the intracellular cAMP and cGMP levels, leading to vascular smooth muscle relaxation in the pulmonary vascular bed.⁷

Despite the fact that we have limited knowledge of Sildenafil safety and use it is still used due to limited choices neonatologists have.⁸ Therefore, Sildenafil 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.⁹ Meconium aspiration syndrome is one of the most important causes of morbidity and mortality in PPHN and this was also found in our study population.¹⁰ Neonates admitted with PPHN in our unit responded to oral sildenafil therapy as evident by decrease in the fractional inspiratory Oxygen demand. The underlying pathology involves hypoxemia due to elevated pulmonary vascular resistance so pulmonary vasodilation is the aim of medical management of PPHN.¹¹

CONCLUSION

The findings of our 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 as was demonstrated in our study. Its role as a pulmonary vasodilator helps in decreasing the right to left shunt and improves the pulmonary blood flow. Thus authors conclude that sildenafil is a very useful and affordable modality for use in PPHN but our study could not adequately rule out the possibility of side effects associated with sildenafil use.

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