Sildenafil for pulmonary hypertension in non-ventilated preterm babies

S Daga, B Verma, C Valvi

Citation

S Daga, B Verma, C Valvi. *Sildenafil for pulmonary hypertension in non-ventilated preterm babies*. The Internet Journal of Pediatrics and Neonatology. 2007 Volume 8 Number 1.

Abstract

Background: Persistent pulmonary hypertension of the newborn (PPHN), a disease of diverse aetiologies, characterized by suprasystemic pulmonary vascular resistance causing a right-to-left shunt, marked hypoxemia and acidosis. Currently ventilatory support and vasodilators form the mainstay of treatment for PPHN. A non-ventilatory approach is most often the only option available in resource- limited setting.

Objective-To study the effect of oral sildenafil as a treatment for PPHN in a resource-limited setting.

Study design: Observational case study

Methods – Six non-ventilated preterm neonates presenting as respiratory distress were studied. They had an increased pulmonary artery pressure and a bi-directional or right-to-left shunt. They received oral sildenafil 0.5mg/kg/dose/12h. Clinical and echocardiographic findings before and after the treatment were compared.

Results- A favourable clinical and echo-cardiographic response was observed in 5/6 neonates. One neonate died.

Conclusion- Oral sildenafil is useful in the treatment of PPHN in preterm neonates, when non-ventilatory treatment is the only available option.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a complex syndrome characterized by increased pulmonary vascular resistance (PVR) resulting in right-to-left shunting across the fetal channels. PPHN may be primary or secondary to a variety of conditions including intrapartum asphyxia, infection, pulmonary hypoplasia, and congenital heart disease. The incidence of PPHN is reported to be 0.43 - 6.8% / 1000 live births and the mortality related to PPHN is to the tune of 10 – 20 % ([1]). A range of advanced modalities such as high frequency ventilation (HFV), surfactant instillation, inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO) are available for management of PPHN. These expensive and/or invasive modalities are unavailable in the developing countries where the frequency and mortality of PPHN is likely to be much higher due to higher incidence of asphyxia and sepsis. We have successfully used intravenous low-dose magnesium sulphate in non-ventilated term neonates with PPHN, balancing the risk of respiratory depression with benefits of vaso-dilatory effect ([2]). Preterm neonates are at a high risk for respiratory depression due to magnesium sulphate. Oral sildenafil may therefore be preferable as a treatment for PPHN in this high-risk population. We wish to report our observations on use of sildenafil in the treatment of PPHN in a group of non-ventilated preterm.

PATIENTS AND METHODS

The study was done at the neonatal unit of Cama and Albless Hospital, Mumbai. The subjects were six preterm neonates with gestation between 31- 37 weeks and birth weight between 1.3–2.7 kg. All presented with respiratory distress. Three presented at birth, two on day 3–4, and another on day 8. One baby had perinatal asphyxia. None had meconium stained liquor. Management included oxygen by head-box, antibiotics, minimal handling, sedation and circulatory support with adrenaline 0.1mcg/kg/min, dobutamine 10

mcg/kg/min and milrinone 0.75 mcg/kg/min. Sildenafil was administered in a dose of 0.5mg/kg/dose/12 h, through an orogastric tube. Full blood count, chest X ray and venous blood gas analysis were performed. Pulmonary artery pressure (PAP) was estimated using a portable Doppler echocardiography machine (Esaolebiomedica SIM 5000 D plus). Normalisation of SPO2 without supplementary oxygen and significant improvement in respiration were taken as clinical indicators of improvement. Echocardiogram was repeated in absence of clear improvement in the clinical status.

Results : Blood counts suggested sepsis in all the 6 neonates. Venous blood gas showed metabolic acidosis (pH < 7.3) in four cases. Chest X ray were non-contributory. Echocardiography before sildenafil revealed following findings : PAP was in the range of 75 – 37 in five neonates. Right-to-left shunt was observed in three and bi-directional shunt in two neonates. Other findings included dilatation of all chambers in one case and dilatation of right atrium, right ventricle, and pulmonary artery in another. One neonate had, in addition, left ventricular dysfunction in the form of hypocontractility with fractional shortening of 30 % and left ventricular stroke volume index of 1.2 ml / kg. Repeat echocardiography after starting sildenafil documented a decline in PAP in three neonates (46 to normal, 55 to normal and 75 to 48). Repeat echo was not required in two neonates. Three neonates required oxygen for 10-15 days while two (twins) required it for 44 days. Case 5 was a preterm vaginal breech delivery. She had persistent respiratory distress and was oxygen-dependent. Echocardiography and blood counts performed on Day 24 were non-contributory. On Day 30, respiratory distress increased. Echocardiogram was repeated. PAP increased to 42 mm Hg and Tricuspid regurgitation appeared. Blood count strongly suggested sepsis. Sildenafil was started and the neonate responded within the next 10 days. One neonate died within 24 hours of birth, she had severe PPHN (PAP: 74mm Hg) and left ventricular dysfunction. Repeat echocardiogram could not be performed. Duration of Sildenafil therapy in our study ranged from 8 to 35 days.

Figure 1

Table 1 : Patient profiles

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gestational age (weeks)	33	32-34	36	35-36	31-32	31-32
Birth weight (kg)	2	1.5	2.2	2.7	1.380	1.8
Age of presentation	Day 4	Day 8	Birth	Day 3	Birth	Birth
Respiratory distress	Severe	Mild	Moderate	Moderate	Moderate	Moderate
Sepsis(Blood counts)	Yes	Yes	Yes	Yes	Yes	Yes
Age, when off oxygen supplementation	10 days	12 days	15 days	11 days	44 days	44 days
Outcome	Expired	Survived	Survived	Survived	Survived	Survived

Figure 2

Table 2 : Echo-cardiographic findings before and after sildenafil

	Pre-sildenafil		Post-sildenafil	
	PAP	Shunt	PAP	Shunt
Case 1	74	Right to left	**	**
Case 2	37	--	NR	--
Case 3	38	Right to left	Normal	--
Case 4	55	Bi-directional	Normal	--
Case 5	42	Right to left	30 later NR*	--
Case 6	75	Bi-directional	53 later NR	--

** Expired within 24 hours. Repeat echo not done. NR = Not required, clinical improvement observed.

DISCUSSION

PPHN is a potentially fatal complication of the circulatory maladaptation. It leads to profound hypoxaemia secondary to right-to-left shunting across the foramen ovale and / or ductus arteriosus as a result of increased PVR. Treatment of PPHN is aimed at maximizing pulmonary blood flow and minimizing PVR without compromising cardiac output. A range of therapeutic options are available for the management of PPHN including. ECMO, HFV, surfactant and iNO. Not all of them are free from significant adverse effects. The high cost of these technically demanding modalities is the main concern for developing countries. Inability to provide and maintain the required training and expertise is also an issue. Phosphodiesterase (PDE) inhibitors have a role in the management of PPHN because they stabilize cGMP, the second messenger of endogenous nitric oxide. PDE type 5 (PDE5) hydrolyses cGMP in the

lung thereby modulating cGMP-mediated pulmonary vasodilatation. Sildenafil appears the most promising of PDE inhibitors ([3]). Evidence from animal studies ([4,5,6]) and reports on its use in children and newborns ([7,8,9,10,11,12]) support this view. Results of studies in animal model of acute and neonatal pulmonary hypertension indicate sildenafil to be a selective pulmonary vasodilator when given orally, as an intravenous infusion ([6]) or in an aerosolized form ([4]). Data on use of sildenafil in PPHN is currently limited to a few case reports ([8], [9]) , small series ([10,11]), and a recent small pilot randomised controlled trial ([7]) and pharmacokinetic data for optimal dosage is also limited. Baquero et al ([7]) have reported the results of their pilot RCT evaluating effect of oral sildenafil on oxygenation in severe PPHN in neonates with gestation >35.5 weeks and oxygenation index (OI) >25. The sildenafil solution was prepared from a 50-mg tablet. An orogastric tube was used to give the first dose of sildenafil (1 mg/kg) or placebo within 30 minutes after randomization and every 6 hours. The median age at treatment was 25 hours. OI improved within 6-30 hours in all neonates who received sildenafil, none had noticeable effect on blood pressure. Survival was significantly higher (6/7 vs 1/7) in those receiving sildenafil. These encouraging results justify the need for a large RCT of sildenafil in PPHN in term/near term neonates. The biological half-life of sildenafil is relatively short. An increase in dose beyond 0.5mg/kg/dose/ 12h was not required in our study and no significant adverse effects were noted in the short-term. To conclude, oral sildenafil (0.5mg/kg/dose/ 12h) may be a safe and effective treatment for PPHN in non-ventilated preterm neonates. Importance of long-term follow up is emphasized.

CORRESPONDENCE TO

Chhaya Valvi Lecturer Department of Pediatrics, B.J. Medical College and Sassoon General Hospital, Pune – 411001 e-mail : chhayavalvi@rediffmail.com

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Author Information

S.R. Daga
Department of Pediatrics, B.J. Medical College and Sassoon General Hospital

Bela Verma
Department of Pediatrics, B.J. Medical College and Sassoon General Hospital

Chhaya Valvi
Department of Pediatrics, G.T. Hospital