Original Paper

Sildenafil in Pulmonary Hypertension Associated with Bronchopulmonary Dysplasia: Friend or Foe?

IRINA BRANESCU[1,2], SIMONA VLADAREANU[1], SANDEEP SHETTY[2], DRAGOS OVIDIU ALEXANDRU[3], ANAY KULKARNI[2,4]

[1]*Carol Davila University of Medicine and Pharmacy Bucharest, Romania*

[2]*St. George's University Hospital, St George's University, London, UK*

[3]*University of Medicine and Pharmacy of Craiova, Romania*

[4]*Royal Brompton Hospital NHS Foundation Trust, London, UK*

ABSTRACT: *Introduction*: Sildenafil is a phosphodiesterase-5 inhibitor used to treat pulmonary hypertension, although its efficiency remains disputed in the neonatal population. We aimed to assess the clinical use of this drug in extremely premature infants diagnosed with pulmonary hypertension associated to bronchopulmonary dysplasia. *Study design*: This is a retrospective study of 18 patients born at ≤ 32 weeks gestational age with pulmonary hypertension complicating moderate to severe bronchopulmonary dysplasia, which was diagnosed on echocardiography at 36 weeks corrected gestational age. Median corrected gestational age at starting sildenafil was 48 weeks (range 32-60). In 4 cases there was a period of > 2 weeks between the evidence of moderate-severe pulmonary hypertension and starting sildenafil. In all other cases it was started as soon as the diagnosis was suspected or confirmed. *Results*: All infants tolerated the use of sildenafil. However, 5 babies (26.31%) died despite ongoing intensive care, and 5 babies (26.31%) died after having care redirected due to severe chronic lung disease (1 due to co-existing neurological abnormality), with on overall mortality of this study of 52.62%. Eight babies (42.1%) survived: 5 continued on sildenafil until hospital discharge, 1 continued on transfer to the paediatric intensive care unit and 2 stopped while inpatients. Upon follow up to 2 years of age, out of the 5 patients who continued upon hospital discharge, 4 stopped at 6, 7, 12 and 18 months respectively, with 1 child being lost to follow up. Two patients (10.52%) restarted sildenafil use later in childhood. Echocardiographic evidence of improvement was noted in 58% (11 cases), with no improvement in 6 cases (32%) and incorrect original diagnosis in 1 case (5%). One infant died less than a week from the initiation of treatment. *Conclusion*: sildenafil use showed no clinical improvement of pulmonary hypertension complicating moderate to severe bronchopulmonary dysplasia in extremely premature infants.

Keywords*: bronchopulmonary dysplasia, pulmonary hypertension, sildenafil, echocardiogram*

Introduction

Despite the current advances in neonatal practice and technology, bronchopulmonary dysplasia (BPD) can affect up to 46% of the extremely premature infants, correlating with impaired short- and long-term outcomes [1-2]. In addition, pulmonary hypertension (PH) represents a significant complication of BPD, with a prevalence estimated to 17-25% for the moderate - and up to 37% in the severe forms of BPD [3-5]. Various strategies have been suggested in order to minimise the associated lung injury, as well as aiming to shorten hospital stay and improve survival rates [6].

It is well established that sildenafil acts as a vasodilator at the intercellular pulmonary arterial level by increasing cyclic guanosine monophosphate (cGMP), and thus has been approved as an efficient treatment of PH in the adult population [7-8]. Current literature indicates significant improvement of the oxygenation index and better survival rates for the sustained pulmonary hypertension treated with sildenafil in the newborn [9-13]. Therefore, it has been suggested that phosphodiesterase -5 inhibitors (PDE5), such as sildenafil, could potentially reduce the pulmonary vascular resistance (PVR) noted in extremely premature infants diagnosed with bronchopulmonary dysplasia complicated by persistent pulmonary hypertension (BPD-PH). Nevertheless, there is very little evidence-based medicine supporting standardised use of sildenafil in preterm infants with BPD-PH. Adverse effects of sildenafil described in the preterm infants encompass significant decrease of estimated pressures in the pulmonary arteries with no changes on the respiratory indices for the short-term [14]. Despite these findings, there is good tolerance of the drug on the long-term use and improved echocardiographic findings [15].

Given the lack of randomised controlled trials in current literature, sildenafil continues to be regarded as a controversial treatment option of pulmonary hypertension in extremely premature

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infants diagnosed with BPD. We hope to add value to the current knowledge available on this 'hot topic' by describing our unit's experience regarding the use of sildenafil in the extremely premature infants.

Methods

Study design and data collection: this is a retrospective study done on the Neonatal Intensive Care Unit (NICU) at St George's University Hospital in London, UK, which is a 42-bed tertiary neonatal unit that admits approximately 100 extremely low birth weight infants every year. This study was registered locally as audit/practice evaluation study.

All infants receiving oral sildenafil between 2010 and 2020 were identified from each patient's electronical medical records. The population of interest was consistent with infants less than 32 weeks gestational age with pulmonary hypertension associated to moderate to severe bronchopulmonary dysplasia (MSBPD). Infants with major abnormalities were excluded from this study.

BPD was defined as per ANZNN (Australia and New Zealand Neonatal Network) guidance: chronic lung disease with ongoing need for respiratory support in the form of continuous positive airway pressure or mechanical ventilation at 36 weeks postmenstrual age (PMA).

Pulmonary hypertension was diagnosed on echocardiogram as the presence of 1 out of the following 3 criteria: tricuspid regurgitation (TR) > 3m/s (equal to pulmonary artery systolic pressure of ≥ 40mmHg) or bidirectional intra-extra cardiac shunt or intra ventricular septal flattening seen at any stage of the cardiac cycle. Once PH was identified we sub-categorized PH into severe and less than severe forms, with the first being characterized by a tricuspid regurgitation (TR) jet > 4m/s, intraventricular septal flattening present throughout the cardiac cycle or by the presence of bidirectional shunting at the level of atrial/ventricle/ductal level.

Cases were selected and reviewed for data collection using the electronic data base for medical records. Baseline characteristics incorporate gestational age at birth, gender, birth weight, the presence of intra-uterine growth restriction, oligohydramnios, chorioamnionitis, full course of antenatal steroids, type of treatment for persistent ductus arteriosus, positive blood culture and diagnosed necrotising enterocolitis. The concomitant use of other pulmonary hypertension medication included inhaled nitric oxide and steroids was also noted. Specific drug data collected were type of respiratory support at the time of diagnosis and gestational age when sildenafil treatment was commenced.

The primary outcome was echocardiographic improvement in pulmonary hypertension. Any evidence of improvement in either calculated pulmonary artery pressure or indirect signs of pulmonary hypertension was counted. Secondary outcomes included survival and age at discharge.

There is no current consensus or known standardised guideline for the diagnosis or treatment of pulmonary hypertension in infants with moderate to severe bronchopulmonary dysplasia. Clinical management of the preterm infants was conducted using a multidisciplinary approach that included paediatric cardiology, long term ventilation strategies, nutritionists, dieticians, gastroenterology, general surgeons, and the pulmonary hypertension team as per local network policy.

All echocardiograms were performed and interpreted by 2 observers accredited in Paediatric Echocardiography and were reviewed by paediatric cardiologists.

Statistical analysis: non-normally distributed data was reported as medians with interquartile ranges, whilst normally distributed variables were reported as means with standard deviations. The impact of pulmonary hypertension associated with sildenafil treatment, was assessed using the Chi-square test/ Fisher's exact test for the distribution of categorical variables. Statistical significance was agreed at < 0.05.

Results

A total of 268 infants with MSBPD were identified during the study period. Out of these, 18 patients received Sildenafil, and 34 had pulmonary hypertension (PH).

Eighteen patients were included in this study. All infants had moderate to severe bronchopulmonary dysplasia in the absence of all major congenital abnormalities. Median gestational age at birth was 24 weeks (range 23-29), mean birth weight was 602g (range 390-750g). Nine infants were male (47.36%) and five infants had intra-uterine growth restriction (26.31%). Ten infants received full antenatal steroids (52.63%), with no antenatal steroids' coverage in 15.78% of the cases (3). Chorioamnionitis was diagnosed in 42% of the cases (8), with maternal intra-abdominal sepsis diagnosed in 2 cases. Baseline characteristics are presented in Table 1.

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Table 1. Baseline characteristics (n = 18)

Gestational Age (weeks)	24 (23-29)
Birth weight (grams)	602 (390-750)
Gender, male (%)	10 (52.63%)
Intra uterine growth restriction (%)	5 (26.31%)
Oligohydramnios (%)	1 (5.26%)
Chorioamnionitis (%)	8 (42.10%)
Full course of antenatal steroids (%)	16 (84.21%)
Postnatal systemic steroid treatment (%)	10 (52.63%)
Inhaled Nitric Oxide (%)	7 (36.84%)
Patent ductus arteriosus (PDA) (%)	6 (31.57%)
Medically treated PDA (%)	4 (21.05%)
Surgically and medically treated PDA (%)	4 (21.05%)
Positive blood cultures (%)	15 (78.94%)
Necrotising enterocolitis (%)	7 (36.84%)

Mechanical ventilation was required for a median of 65 days (range 8-198 days) with 5 cases (26%) on high flow nasal cannula oxygen at 36 weeks corrected gestational age, 2 (11%) cases on BiPAP. Majority of cases (32%) were on CPAP at 36 weeks cGA. Eight infants (42.10%) survived till discharge. Five babies died of due to terminal respiratory failure or progressive right heart failure, while care was redirected due to the severity of the chronic lung disease in 4 cases, with one infant died of co-existing neurological impairment (Figure 1).

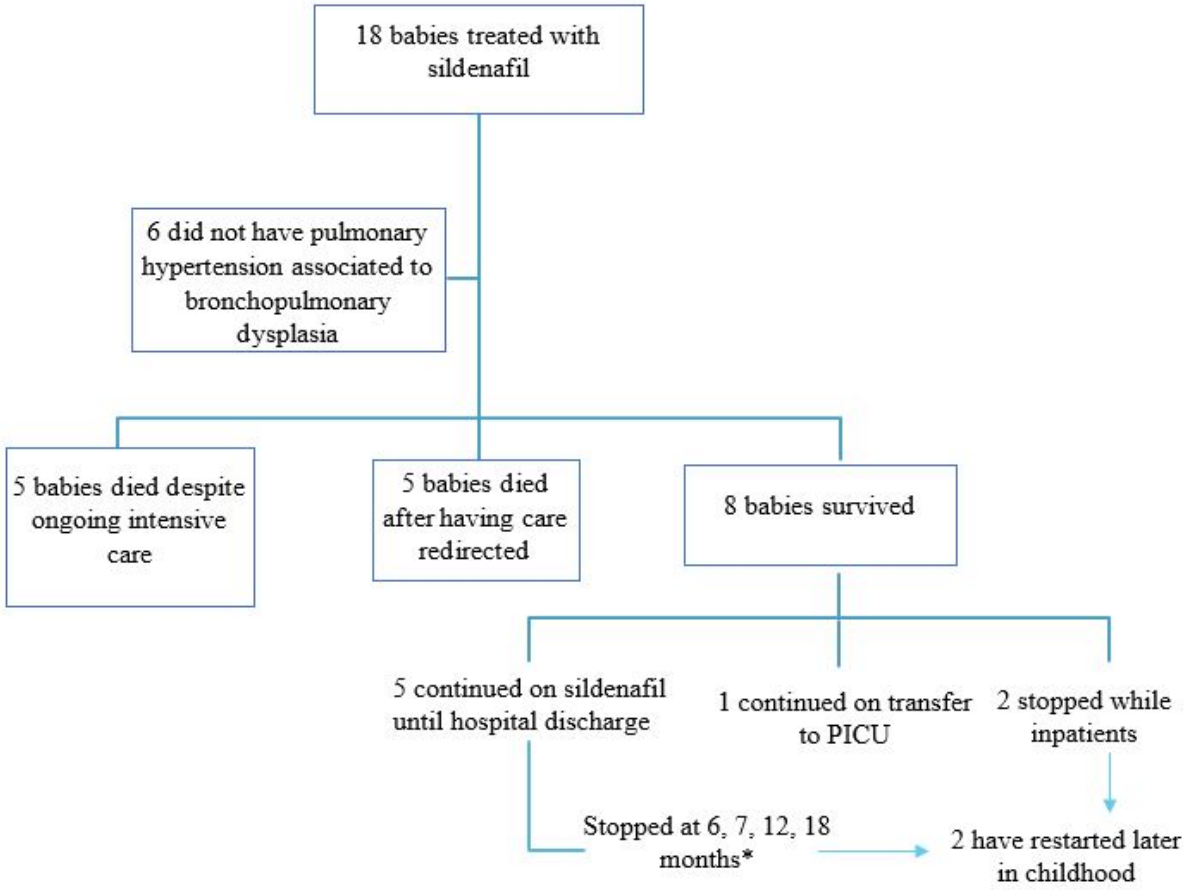

Figure 1. Flowchart of the overall outcomes

An echocardiographic response was observed in 58% of the cases with any evidence of improvement noted in either calculated pulmonary artery pressure or indirect signs of pulmonary hypertension. One case had no echocardiographic evidence of pulmonary hypertension, but ECG showed right ventricular hypertrophy with worsening respiratory status, therefore sildenafil was commenced. Echocardiography screening was not available in one case with clinical evidence of pulmonary hypertension who responded to inhaled nitric oxide. Severe pulmonary hypertension was diagnosed on echocardiography in 58% of the cases (11 infants) with either systemic or supra-systemic pulmonary artery pressures. Severe pulmonary hypertension was diagnosed via cardiac catheterisation in 5% of the cases, with indirect evidence of PH available in 11% of the cases (unable to measure tricuspid regurgitation, but either right ventricular hypertrophy or severe interventricular septal flattening/bowing were present). Post-natal systemic steroids were used as pulmonary rescue strategy in 10 cases. Five infants had persistent ductus arteriosus (PDA) when Sildenafil treatment was started. Four infants died, whilst 1 had treatment stopped due to worsening left to right shunting. Out of the remaining 14 babies with no PDA present, 10 had duct ligation prior to developing pulmonary hypertension whilst one closed following treatment with ibuprofen.

Analysing the impact of Sildenafil use on patients' bronchopulmonary dysplasia, with, and without pulmonary hypertension, we found that patients who were treated with oral Sildenafil had a higher mortality rate (Table 2). For patients with PH, the result of the Chi-square test was p=0.001585, and for Fisher's exact test it was p=0.0053, both showing a statistically significant difference in respect of the mortality for infants with pulmonary hypertension treated with Sildenafil. On the other hand, for patients without PH, Chi-square p=0.160648 and Fisher's p=0.2533, both results being greater than the maximum significance level that shows a difference between patients treated or not with Sildenafil. This should not be interpreted as Sildenafil having a negative impact on survivability, but as Sildenafil being reserved for critically ill patients.

Table 2. The impact of Sildenafil on mortality

BPD - PH	Sildenafil	Died	Survived	Total
With PH	Sildenafil +	8 (66.67%)	4 (33.33%)	12 (100.00%)
	Sildenafil -	3 (13.64%)	19 (86.36%)	22 (100.00%)
Without PH	Sildenafil +	1 (16.67%)	5 (83.33%)	6 (100.00%)
	Sildenafil -	10 (4.39%)	218 (95.61%)	228 (100.00%)

Discussions

Our study group received oral sildenafil starting at 0.5mg/kg every 6 hourly to a target maintenance dose of 2mg/kg every 6 hourly, with a median time to reach the maximum dose of 10 days.

The difficulty in interpreting the efficacy of sildenafil use can be explained by several factors. Mainly, by the fact that there is no current consensus on best clinical practice and predictors of clinical outcomes for this entity. Respiratory severity scores have been studied in this direction but were unable to provide predictable value. Oxygenation Index (OI) is most commonly used to assess clinical improvement of pulmonary hypertension. The use of NTproBNP in conjunction with echocardiographic screening might provide better clinical value. Nevertheless, there is no current consensus on the reference values of NTproBNP in the preterm population. In addition, we need to bear in mind that accurate continuous arterial blood sampling is difficult to achieve in the preterm infants due to nature of difficult vascular access and frequent complications associated with this invasive measurement. Moreover, repetitive arterial punctures are not indicated as they carry a great deal of risks.

In addition, 36.84% of cases (7) were receiving inhaled nitric oxide at the introduction of sildenafil. Results may have been contaminated and thus leading to less notable effects and underestimated clinical response from the PDE5 treatment.

Another predicament consists of the long-time used to reach maximal sildenafil dose. Therefore, it can very well be that the time frame used to

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assess for sildenafil efficiency, overrun with increasing dosage, hence leading to an underestimation of the clinical response. Nyp et al hypothesized in a comparable study that the reduced clinical results could be due to the ventilation/perfusion mismatch that is to be expected within the first stages of sildenafil treatment [14].

During our study, the echocardiography assessment was done at the beginning of therapy, with follow up imaging done at day 10 and then monthly. More frequently echocardiograms would have potentially provided with a better assessment of the response to sildenafil treatment.

Cardiac catheterization remains the gold standard for the diagnosis and assessment of pulmonary hypertension [15-16]. However, this is not a routine practice in the neonatal world, due to how highly invasive this procedure is for this target population [17]. Notwithstanding, the recommendation for cardiac catheterization before starting any targeted therapy for pulmonary hypertension remains. Having said that, previous studies highlighted echocardiography as a reliable non-invasive alternative for correct diagnosis of pulmonary hypertension compared to the gold standard, with a sensitivity of 67% and positive prediction value of 69%, but correctly assessing the severity in only 47% of cases [18].

In our study we used a median dose of 1mg/kg/day, with gradual increments aiming to avoid systemic low blood pressure which is a commonly known side effect of sildenafil. This practice is used by most institutions, although the current data available on this particular side effect is conflicting, with few reported significant incidences. In clinical practice, preterm infants needing PGDE 5 inhibitors are likely to require vasoactive agents to support their systemic blood pressure at the time of sildenafil initiation and perhaps masking this side-effect. Nevertheless, blood pressure was routinely monitored during induction and every time sildenafil dose was increased, with transient hypotension, and no major events documented. Sildenafil treatment was stopped in two cases, one not related to side effects, but due to good clinical response on inhaled nitric oxide use and a second one due to worsening left to right shunting through the PDA.

The retrospective design and small sample size are the main limitations of our study. In addition, nearly 40% were receiving inhaled nitric oxide before starting sildenafil, which may have underestimated the effectiveness of the treatment. Moreover, it was not possible to identify a group of infants with BPD-PH not treated with sildenafil as control, since there is no routine screening done in our unit for PH in infants who are suffering from bronchopulmonary dysplasia. It would have been interesting to be able to make that comparison.

Of note is that our cohort included moderate to severe bronchopulmonary dysplasia cases with significant respiratory disease, where a multidisciplinary management approach was being used. This included targeted oxygen delivery, optimised nutrition, treatment of symptomatic gastro-oesophageal reflux with naso-jejunal enteral feeds, treatment of upper airway abnormalities and individual use of pulmonary vasodilators, and thus limiting the generalizability of this study.

Conclusion

Sildenafil treatment in patients with pulmonary hypertension complicating moderate to severe bronchopulmonary dysplasia was not associated with improved mortality rates. Sildenafil dosage used in our centre is according with the current literature. Future research with robust longitudinal or randomized controlled design is still needed.

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Corresponding Author: Simona Vladareanu, Carol Davila University of Medicine and Pharmacy Bucharest, Romania, e-mail: simona.vladareanu@umfcd.ro

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