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Sildenafil use in premature infants with bronchopulmonary dysplasia and pulmonary arterial hypertension

A. Study Purpose and Rationale

Introduction
Pulmonary arterial hypertension (PAH) is a serious condition that if left untreated can result in right heart failure and death. There are many etiologies of PAH and while in adults, idiopathic pulmonary hypertension is the most common, the etiology of PAH in children is more frequently associated with congenital heart disease or hypoxic conditions. In neonates, pulmonary hypertension is classified as persistent pulmonary hypertension of the newborn (PPHN) or PAH associated with chronic lung disease of prematurity, or bronchopulmonary dysplasia (BPD). The etiologies of these two types of PAH are different and therefore effective treatment for each is likely to be different. In this study, we will focus on the treatment of patients with BPD and PAH.

Bronchopulmonary Dysplasia
Infants born prematurely and with low birth weight are at increased risk of developing BPD due to immature lung development.[1,2] The pathology and manifestations of BPD have changed in recent years since the introduction of surfactant into the care of neonates and advances in the support of extremely premature infants leading to increased survival. BPD is now most common in infants born at 24-28 weeks gestational age.[3] The clinical definition of BPD in the post-surfactant era is still debated. Traditionally, BPD was defined as the need for supplemental oxygen or respiratory support at 36 weeks post-gestational age.[4] The NIH definition for "new" BPD requires that infants have supplemental oxygen requirements for at least 28 days after birth.[5] BPD is further divided into mild, moderate and severe based on oxygen requirement at 36 weeks post-gestational age for infants born at less than 32 weeks or at 56 days postnatal age for infants born at greater than 32 weeks.[6] However, they recognize that thresholds for supplemental oxygen and respiratory support such as continuous positive airway pressure (CPAP) vary among institutions and thus, which infants qualify as having BPD will change depending on where they are treated.

Bronchopulmonary dysplasia and pulmonary arterial hypertension
"New" BPD is thought to be the result of impaired post-natal lung growth with decreased alveolar and vascular growth as the predominant features.[5,7] Premature infants with BPD are at risk of developing respiratory sequelae and respiratory failure due to impaired alveolar growth, but they are also at risk of cardiovascular sequelae, including PAH. The acute lung injury that occurs as a result of premature birth leads to narrowing of the vessels and decreased compliance and well as alterations in the vasoreactivity of the vessels and these changes lead to increased pulmonary vascular resistance (PVR).[1] This increase in PVR leads to right ventricular hypertrophy and secondary changes to the left heart and changes in catecholamine levels.[8] Some of these patients will develop increased pulmonary artery pressure (PAP) and PAH.[3]

The incidence of pulmonary hypertension in patients with BPD is thought to be around 22-25%.[9,10] Patients with both BPD and PAH have increased morbidity and mortality compared to patients with BPD alone.[11] In 2007, Khemani et. al studied 42 premature babies with BPD and PAH and demonstrated that those patients with severe PAH (RV pressure ≥100% systemic pressure) at any time during the study had significantly decreased survival times compared to those patients with less severe PAH.[12] At this time, there is no clear data to indicate which patients with BPD should be screened for PAH and what level of

increased PAP leads to clinically significant outcomes.[3] Although the relationship between severity of PAH and mortality is not completely understood, there is evidence that increased PA pressure contributes to decreased survival in patients, providing a rationale for therapies that could potentially reduce the PAP in these patients.

Natural history

The clinical course of patients with BPD and PAH seems to differ from patients with idiopathic pulmonary hypertension and other forms of secondary PAH.[13] Most patients with BPD and PAH show some improvement in PAH over time.[9,12] One study assessed PAP as determined by echocardiography in premature patients with CLD compared to healthy preterm infants and showed increased PAP in the group with CLD compared to controls at all time points but both groups showed a decrease in their PAP throughout the first year of life.[14] Although SGA and more severe PAH seem to be predictors of decreased survival, it is unclear which patients with BPD and PAH will improve spontaneously and which will develop severe complications.[12]

Treatment

The treatment for patients with BPD and PAH is not clearly defined and there is limited data to show that interventions improve long-term outcomes. Goals of treatment include increasing survival, particularly in those patients with severe PAH, as well as minimizing exacerbations and supporting pulmonary growth and development.[12] Routine treatment involves proper nutrition, respiratory management, pH balance and avoidance of respiratory infections.[3,8] Data on targeted treatment of the pulmonary hypertension is lacking. Several studies have demonstrated a decrease in PAP in patients with BPD and PAH receiving supplemental oxygen therapy and long-term therapy with supplemental O2 may be necessary in these patients to help promote lung development by minimizing hypoxic episodes.[15] Whereas infants with CLD are frequently managed with oxygen saturations in the low 80s, recommendations for those with PAH include maintaining saturation at 90-92%.[8] However, this must be balanced with the potential detrimental effects of increased oxygen saturations in premature patients.[12] Inhaled nitrous oxide (iNO) has also been shown to acutely lower PAP in these patients and is often used as a component of the treatment regimen.[12,16]

In adults and children with idiopathic pulmonary hypertension, vasodilators are the treatment of choice. However, none of the medications that are approved for use in adults are approved for use in children in the US. Although in theory it makes sense to use vasodilators as targeted therapy for patients with PAH and BPD, there have not been prospective trails to assess their use and there are risks of using vasodilators in patients who may have other associated cardiac or pulmonary anomalies.[3] Given that there is some evidence that PAH may improve without intervention and that there is not clear evidence to show that vasodilators are safe and effective in neonates with BPD, it is unclear who, if anyone, should be treated with them.[13]

Sildenafil, a selective type 5 phosphodiesterase inhibitor is a vasodilator that can be administered orally and is frequently used in adults and children with idiopathic pulmonary hypertension and therefore seems like a good choice for patients with BPD and PAH. In addition to vasodilation, it is thought that PDE-5 inhibitors might also act at a cellular level to decrease progression of the vascular disease that is the underlying cause of PAH and cause reversal of inflammation and vascular remodeling.[8] In 2005, Galiè et. al published results from the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-1 trial which showed that in adult patients (>18 years) with symptomatic PAH who were randomized to receive sildenafil had improved exercise capacity, WHO functional class and hemodynamics after 12 weeks of therapy compared to those who received placebo and that the drug was well-tolerated.[17] There has only been one small randomized controlled trial of sildenafil in children that was done in infants with PPHN which showed some improvement in gas exchange but was too small to assess for adverse outcomes and survival.[18] Two small retrospective studies have looked at the use of sildenafil in preterm infants with

BPD and there have been several case reports published.[19,20] Nyp et. al studied 21 patients with BPD and pulmonary hypertension and showed a decrease in estimated RV peak systolic pressures after starting sildenafil but could not demonstrate an improvement in gas exchange. The mortality rate in these patients was 19% at 12 months which is lower than reported mortality for infants with BPD, but given that there were no controls, the effect of sildenafil on mortality could not be demonstrated.[19] Mourani et. al studied 25 patients who had been treated with sildenafil and similarly found a significant decrease in estimated sPAP in patients who has measurements before and after therapy with a majority of patients showing some improvement in echocardiographic assessment of PAP after starting sildenafil.[20] Both studies showed few adverse effects of sildenafil and demonstrated a need for larger trials. Given that we have now been using sildenafil in patients with BPD and PAH in our NICU since about 2005, we believe that we will be able to identify more patients treated with sildenafil than prior studies giving us an advantage in terms of the significance of our data.

Despite the increased morbidity in patients with PAH and BPD, there have been few clinical trials examining the safety and efficacy of pulmonary vasodilators in these patients. Barriers to clinical trials include difficulty identifying clinically meaningful outcomes in pediatric patients, recruiting sufficient numbers of patients, the need for long-term follow-up to assess neurodevelopmental outcomes and side effects and ethical concerns surrounding infants and children in clinical trials, particularly when evaluation involves tests such as cardiac catheterization and echocardiography which may require sedation.[21] In addition, there was recently a recommendation issued by the FDA that said that sildenafil should not be used in children age 1-17 based on data suggesting increased mortality in patients taking high dose sildenafil for idiopathic PAH or PAH secondary to congenital heart disease.[3,22,23] This recommendation does not specifically mention treatment in patients under 1 year and members of the pediatric pulmonary hypertension network published a report cautioning against this warning and suggesting that high doses of sildenafil should be avoided but that there is evidence of benefit of sildenafil at low doses in these patients and that further data is needed.[24]

Although there is significant need for prospective trials of sildenafil and other vasodilators in infants with BPD and PAH, given these limitations, additional retrospective analysis on the use of vasodilators including sildenafil may be helpful in establishing initial safety and efficacy data and providing more justification for prospective randomized trials. Thus, we aim to report our experience using sildenafil in premature infants with BPD and PAH to assess their baseline characteristics and clinical outcomes in order to assist in the process of deciding whether randomized trials are warranted and ethical.

Study Aims

1. To compare the change in estimated systolic pulmonary artery pressure (PAP) measured by echocardiography in infants treated with sildenafil and controls
2. To report the demographic characteristics of neonates with BPD and pulmonary hypertension treated with sildenafil at our institution as well as sildenafil dosing and treatment duration

Study Hypothesis

Patients with BPD and PAH who received sildenafil will have more improvement in their systolic PAP compared to patients with BPD and PAH who do not receive sildenafil.

B. Study Design and Statistical Analysis

Study Design

We will be performing a retrospective study of neonates with BPD and PAH treated in the NICU at the Morgan Stanley Children's Hospital of New York Presbyterian. We will be reporting on the use of sildenafil in patients with pulmonary hypertension associated with prematurity. Patients will be identified using available billing records from the department of pediatric cardiology and neonatology to identify patients with BPD as well as PAH.

We will review the medical records of the selected patients to obtain demographic characteristics of the infants, birth history including gestational age and prenatal history. We will collect data on diagnoses and treatment approach including timing and dosing of sildenafil therapy as well as any other treatments that were administered. As our primary outcome, we will look at echo parameters of estimated PAP. We will also report measures of RV function from echocardiography. In addition, we will obtain measures of disease severity and the need for additional cardiopulmonary support including the use of iNO, dose and time on iNO, time on mechanical ventilator, CPAP and/or supplemental O2 and the need for inotropic support. We will also look at length of stay and mortality data for these infants although we do not anticipate having enough power to evaluate for mortality. When available, we will also collect data from cardiac catheterization including pulmonary artery pressures.

For our controls, we will use patients diagnosed with BPD and PAH who were not treated with sildenafil. We will attempt to match our controls to the patients who were treated with sildenafil based on gestational age, severity of BPD and severity of PAH. The controls will be patients who have had more than one echocardiogram assessing sPAP.

Statistical Analysis

In order to compare the change in estimated systolic PAP(sPAP) in cases and controls, we will measure the change in sPAP before and after initiation of sildenafil therapy. There is evidence that sildenafil is a fast-acting drug so the minimum time between echocardiograms can be short. We will then calculate the change in sPAP in the controls with a minimum of one month between echocardiograms.

We will use an unpaired t-test to compare the mean change in sPAP in the sildenafil group to the mean change in sPAP in the control group. Based on prior studies, I am assuming that the SD in sPAP is 15mmHg and that the clinically significant difference that we would like to assess for is 10mmHg. The tests will be performed with and power of 0.80.

Given those parameters, we can calculate the necessary sample size using the sample size equation for an unpaired t-test :

$$n = 1 + 16\left(\frac{\text{stddev}}{\text{effect}}\right)^2$$

$$n = 1 + 16\left(\frac{15}{10}\right)^2$$

$$n = 37$$

Thus we will need 37 subjects in each group.

C. Study Procedure

This study will consist of a retrospective review of subjects' medical record. Data collected will include birth history including gestational age at time of birth, prenatal history, diagnoses, pharmacologic treatment, need for supplemental oxygen and respiratory support and echocardiography data. The information collected will only include information documented as part of routine care and there will not be any additional procedures or tests performed on the patients. We anticipate that collection of this data will take about one year.

D. Study Drugs

Although we will be studying the use of sildenafil in our study population, we will not be administering this drug for the purposes of this study. Sildenafil is not currently FDA approved for use in pediatric patients. However, the patients in the study were treated with sildenafil based on prior research and the clinical judgment of the treating physicians and was not in any way influenced by our current study.

E. Medical Device
There will be no medical devices used in this study.

F. Study Questionnaires
There will be no questionnaires used in this study.

G. Study Subjects
The study population includes all patients admitted to the neonatal intensive care unit (NICU) at the Morgan Stanley Children's Hospital of New York who have the diagnosis of bronchopulmonary dysplasia and pulmonary hypertension between the years 2005 and 2013. Patients will be identified based on billing data from the NICU and department of pediatric cardiology. The study will include patients born at our hospital and transferred from outside hospitals. Echocardiography data will be reviewed to confirm the diagnosis of pulmonary hypertension in these patients.

Inclusion criteria for this study will include 1) that the patients were born prematurely at less than 37 weeks gestational age, 2) that they have bronchopulmonary dysplasia defined as having a requirement for supplemental oxygen for at least 28 days[5,6], 3) that they have pulmonary hypertension confirmed by echocardiogram demonstrating RV hypertrophy or estimated systolic PAP >50% systemic or cardiac catheterization.

Patients will be excluded if they have associated congenital heart defects, airway or lung anomalies, congenital anomalies of the pulmonary vessels or were diagnosed with persistent pulmonary hypertension of the newborn (PPHN).

As this study is focused on assessing the use of sildenafil in neonates with pulmonary hypertension, it is necessary to use data from minors which are considered to be a vulnerable population. However, as this is a retrospective chart review, the patients will not be put at any risk by having their data used in the trial.

H. Recruitment of Subjects
This is a retrospective chart review and there will be no active recruitment of patients. Patients will be identified from billing records according to the above criteria. Information will be collected from the patient's electronic medical record.

I. Confidentiality and Study Data
All patient data obtained for study purposes will be de-identified by assigning a unique code to each patient. There will be a separate file containing the codes and any identifying information which will be available only to the study coordinator and primary investigators. All electronic files with patient data will be stored on an encrypted drive that is password protected and is only accessibly to study investigators.

J. Potential Conflict of Interest
There are no potential conflicts of interest in this trial.

K. Location of the study
Columbia University Medical Center department of pediatric cardiology.

L. Potential Risks

There are no potential risks to subjects as a result of their clinical data being used in this study.

M. Potential Benefits
There are no direct benefits to the patients whose data will be used in this study. However, there may be benefits to other children with BPD and pulmonary hypertension if we gain further insight into the safety and efficacy of sildenafil as a treatment option.

N. Alternative therapies
This is a retrospective study in which the patients will already have received sildenafil.

O. Compensation to Subjects
Since this is a retrospective analysis, there will be no cost to the subjects.

P. Costs to Subjects
Since this is a retrospective analysis, there will be no cost to the subjects.

Q. Minors as Research Subjects
This study is retrospective observational study involving data obtained from the medical records of minors. Approval from the Department of Pediatrics Committee on Human Investigation will be received prior to initiation of the study.

R. Radiation or Radioactive Substances
No radiation or radioactive substances will be used in this study.

References

1. Abman SH. Monitoring cardiovascular function in infants with chronic lung disease of prematurity. Arch Dis Child Fetal Neonatal Ed 2002;87:F15-8.
2. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr 2011;23:167-72.
3. Mourani PM, Abman SH. Pulmonary vascular disease in bronchopulmonary dysplasia: pulmonary hypertension and beyond. Curr Opin Pediatr 2013;25:329-37.
4. Stroustrup A, Trasande L. Epidemiological characteristics and resource use in neonates with bronchopulmonary dysplasia: 1993-2006. Pediatrics 2010;126:291-7.
5. Kinsella JP, Greenough A, Abman SH. Bronchopulmonary dysplasia. Lancet 2006;367:1421-31.
6. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
7. Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Hum Pathol 1998;29:710-7.
8. Krishnan U. Management of pulmonary arterial hypertension in the neonatal unit. Cardiol Rev 2010;18:73-5.
9. An HS, Bae EJ, Kim GB, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 2010;40:131-6.
10. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics 2012;129:e682-9.
11. Goodman G, Perkin RM, Anas NG, Sperling DR, Hicks DA, Rowen M. Pulmonary hypertension in infants with bronchopulmonary dysplasia. J Pediatr 1988;112:67-72.
12. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260-9.
13. Kulik TJ, Rhein LM, Mullen MP. Pulmonary arterial hypertension in infants with chronic lung disease: will we ever understand it? J Pediatr 2010;157:186-90.
14. Subhedar NV, Shaw NJ. Changes in pulmonary arterial pressure in preterm infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2000;82:F243-7.
15. Abman SH, Wolfe RR, Accurso FJ, Koops BL, Bowman CM, Wiggins JW, Jr. Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. Pediatrics 1985;75:80-4.
16. Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. Am J Respir Crit Care Med 2004;170:1006-13.
17. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. The New England journal of medicine 2005;353:2148-57.
18. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. Pediatrics 2006;117:1077-83.
19. Nyp M, Sandritter T, Poppinga N, Simon C, Truog WE. Sildenafil citrate, bronchopulmonary dysplasia and disordered pulmonary gas exchange: any benefits? J Perinatol 2012;32:64-9.
20. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr 2009;154:379-84, 84 e1-2.
21. Adatia I, Haworth SG, Wegner M, et al. Clinical trials in neonates and children: Report of the pulmonary hypertension academic research consortium pediatric advisory committee. Pulm Circ 2013;3:252-66.
22. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation 2012;125:324-34.
23. Administration USFaD. Revatio (sildenafil): drug safety communication - recommendation against use in children. . 2012.
24. Abman SH, Kinsella JP, Rosenzweig EB, et al. Implications of the U.S. Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension. Am J Respir Crit Care Med 2013;187:572-5.