

## The Effects of Sildenafil on the Treatment of Neonatal Chronic Lung Disease

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### Abstract

**Background:** Bronchopulmonary dysplasia is one of the most common disorders in premature infants and this study aimed to investigate the role of sildenafil in the treatment of neonatal chronic lung diseases.

**Methods:** In a placebo-controlled clinical trial study, a total of 40 neonates were included and randomly divided into control and intervention groups; sildenafil tablets were used at a dose of 2mg per kg for 8 hours in the intervention group and placebo with the same characteristics in the control group. After a period of 10 days, oxygen demand, type of respiratory support, changes in pulmonary artery pressure, Length of hospital stay, and systemic blood pressure changes were measured.

**Results:** Duration of admission significantly decreased in the intervention group (P value = 0.006). For the neonates in the control group from approximately 11 days after the start of treatment (11/47±9/19) and for those in the intervention group from approximately 8 days after the start of treatment (8/21±3/84), respiratory support with positive pressure was changed to respiratory support with free flow oxygen. No severe systolic or diastolic blood pressure change was observed in any of the groups. Decrease in pulmonary pressure was significantly higher in the intervention group than that in the control group (21/1% and 68/4%, respectively) (P value: 0.003).

**Conclusion:** The results of the study showed that sildenafil significantly reduced the length of hospital stay, the duration of the need for respiratory support and oxygen administration, and corrected the pulmonary pressure. No specific side effects were found.

**Key Words:** Bronchopulmonary dysplasia (BPD), Chronic Respiratory Diseases, Neonates, Prematurity complications, Pulmonary Arterial Pressure Sildenafil.

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## 1- INTRODUCTION

Premature birth is a leading cause of morbidity and failure to rescue among infants worldwide. Prematurity complications are actually responsible for more than 35 percent of the 3.1 million deaths across the world in a single year, which is only secondary to pneumonia as the leading cause of death in children under 5 years of age (1, 2){Lemons, 2001 #1}. Bronchopulmonary dysplasia (BPD) is a common side effect in very premature infants with an occurrence of 5-68%, which is growing significantly along with reduction in gestational age and birth weight, and affects 30-40% of infants under 1500 g at baseline (3, 4). BPD is also caused by lung damages caused by factors such as maternal intrauterine growth retardation, lack of prenatal corticosteroids, Chorioamnionitis, postpartum ventilation, hyperoxia, or inflammation that causes bronchospastic disease, poor development, and pulmonary artery hypertension (PAH) (2, 5). Initially, BPD was defined as lung injury due to the mechanical ventilation and oxygen therapy, which can be found most commonly in preterm infants born at 28 to 35 weeks of the postmenstrual age (PMA). Advances in neonatal and obstetric care, such as receiving prenatal corticosteroids and surfactant replacement therapy, have led to a change in disease phenotype and have been seen in premature infants who can survive to less than 24-28 weeks of gestation (5). Therefore, the definition of chronic lung disease in the context of impaired alveolar development and the arterial bed of the immature lung is defined according to the need for oxygen at 36 weeks of gestation or the need to receive oxygen for more than 28 days (5).

Chronic lung disease at 36 weeks of age is more likely to be classified as mild (no oxygen supplementation), moderate (less than 30% oxygen supplementation), or severe (oxygen supplementation greater

than 30% and / or need positive pressure support) (6, 7). Despite remarkable advances in prenatal and neonatal care, BPD is one of the leading causes of prematurity complications and has a significant impact on individuals, communities and health resources (8). By increasing the survival of such premature infants, efforts are being made to limit the consequences relevant to BPD. Managing BPD is a major challenge for physicians, and the development of BPD is associated with Delayed brain neurodevelopment and an increased risk of readmission due to respiratory problems. Survivors of BPD usually have respiratory injuries and complications in adulthood (8-12).

Sildenafil is a potent inhibitor of cyclic guanosine monophosphate (cGMP) pathway that elevation of its level in the body eventually leads to a decrease in the intracellular calcium levels and suppression of the proliferation of smooth muscle cells. Thus, in animal models, sildenafil is effective in maintaining angiogenesis, enhancing alveolarization, and right ventricular hypertrophy, inner wall thickness, pulmonary vascular resistance, and inflammatory response, reduction making sildenafil as an attractive option for reducing the pulmonary pressure and enhancing the alveolization and effective drug in controlling the chronic neonatal lung disease (13-14). To determine the positive effect of sildenafil in the control and treatment of chronic lung disease, the effectiveness and safety of this treatment in infants needs further investigations. Due to the fact that the side effects of sildenafil have been shown in different studies, designing a study to identify the efficacy and side effects of sildenafil in infants with chronic lung disease seems necessary to complement the findings of other studies. Also, considering the pathophysiology of different causes of chronic lung disease in preterm infants

and the possibility of different effects of treatment based on etiology, we decided to design a placebo-controlled study in patients with chronic lung disease and investigate the role of sildenafil in the treatment of chronic lung disease.

## 2- METHODOLOGY

After obtaining the approval of the Research Ethics Committee of Tabriz University of Medical Sciences (ethics code IR. TBZMED. REC. 1398.488) and also registering in IRCT with the code (IRCT201601020258), this study was designed as a placebo controlled clinical trial, so that a total of 40 neonates (admitted to Al-Zahra Hospital with a diagnosis of chronic lung disease) were included in the study, observing the inclusion and exclusion criteria. The duration of the study was 12 months, from August 2018 to August 2019. The neonates were divided into control and intervention groups (receiving medication and placebo) by the use of computer randomization based on the Randomiser.org program.

### 2-1. Inclusion and Exclusion criteria

Inclusion criteria included chronic lung disease, neonatal hemodynamic stability (absence of hypotension, peripheral perfusion disorder and tachycardia), absence of gastrointestinal disorders (gastric stasis - abdominal distension and vomiting) and written consent by the patient's parents to participate in the study. Exclusion criteria were the need for oxygen at 36<sup>th</sup> week of intrauterine age for known causes other than chronic lung disease and feeding intolerance (presence of gastric stasis-abdominal distension and vomiting). In each group, neonates were divided into 3 groups of mild, moderate and severe, based on the severity of chronic lung disease and were randomly assigned to the intervention and control groups. Patients were then evaluated for demographic variables such as age and

sex, as well as the severity of the underlying disease and pulmonary artery pressure. All patients underwent routine and necessary care, such as respiratory support and oxygen. After confirming pulmonary pressure increase in pulmonary arteries by echocardiography (EOGE SONO site echocardiography device made in the United States) performed by a pediatric cardiologist, sildenafil 50 mg tablet (Abidi Company) with a dose of 2 mg per kg every 8 hours in the intervention group and placebo in the same shape and same color in the control group began for the neonates. To standardize the drug dissolved in breast milk and non-drug breast milk (placebo group), the infants were given milk at each feeding. The patients were constantly monitored for the possible complications such as systemic hypotension and feeding intolerance. After a period of 10 days, variables such as oxygen demand (FiO<sub>2</sub>), type of respiratory support, pulmonary artery pressure changes (measured by echocardiography), length of hospital stay and systemic blood pressure changes were measured, in patients in the intervention and control groups. In addition, if any serious side effects were observed in the intervention group, sildenafil was discontinued immediately.

Pulmonary pressure below 25 mm Hg was considered as normal pressure, 25 to 40 mm Hg as mild pulmonary pressure, 40 to 50 mm Hg as moderate pulmonary pressure and above 50 mm Hg as severe pulmonary pressure. Pulmonary pressure was measured on the starting day of the treatment (before medication) and 10 days after treatment by a pediatric cardiologist through standard methods.

### 2-2. Data analysis

Data were analyzed using SPSS software version 22. The normality of the data was assessed using the Kolmogorov-Smirnov test. The frequency (percentage) was used to describe the qualitative data and the

median (25th and 75th percentiles) was used for the quantitative abnormal data. Chi-square test was used to analyze the qualitative data and Fisher's exact test was used if there were no conditions for using this test. Independent t-test was used to analyze quantitative data in two normal groups. Also, paired t-tests were used to analyze quantitative data in two time sequences in two normal groups. Statistically significant level was considered as 5%.

### 3- RESULTS

40 neonates were first selected for the purpose of the study, but 2 of them were excluded due to failure to complete the treatment because of parents' dissatisfaction to continue the study. The Demographic and Pulmonary Pressure Characteristics of the participants in the intervention and control groups are compared in **Table 1**. Among all the variables of gender and studied pulmonary pressure status, only the rate of improvement in pulmonary pressure in the intervention group was significantly higher than that in the control group (P-value = 0.003); however, there was no statistically significant difference between the two groups in pulmonary pressure differences on the first day and pulmonary

pressure after the end of the treatment (P-value > 0.05) (**Table 1**) (**Fig. 1** and **2**).

Also, according to **Table 2**, among all variables of patients' conditions and recovery process during the study period, the duration of hospitalization after the start of treatment (P-value = 0.006), the duration of respiratory support in the form of free flow oxygen (P-value = 0.001) and the duration of cessation of respiratory support (P-value = 0.003) in the control group were significantly longer than those in the intervention group; on the other hand, there was no statistically significant difference between the intervention and control groups (P-value > 0.05) in the variables of treatment age, gestational age and duration of Fio<sub>2</sub> reaching 21%.

In the intervention group, all variables of (Fio<sub>2</sub>) (P-value = 0.001), systolic blood pressure (P-value = 0.001), diastolic blood pressure (P-value = 0.001) and heart rate (P-value = 0.029), one day after treatment, were significantly less than those in the first day. Also, in the intervention group, except for the heart rate variable, the other variables of (Fio<sub>2</sub>) (P-value = 0.037), systolic blood pressure (P-value = 0.001) and diastolic blood pressure (P-value = 0.001) after the end of treatment were significantly lower than those on the first day.

**Table-1:** The Comparison of Demographic and Pulmonary Pressure Characteristics of the intervention and control groups

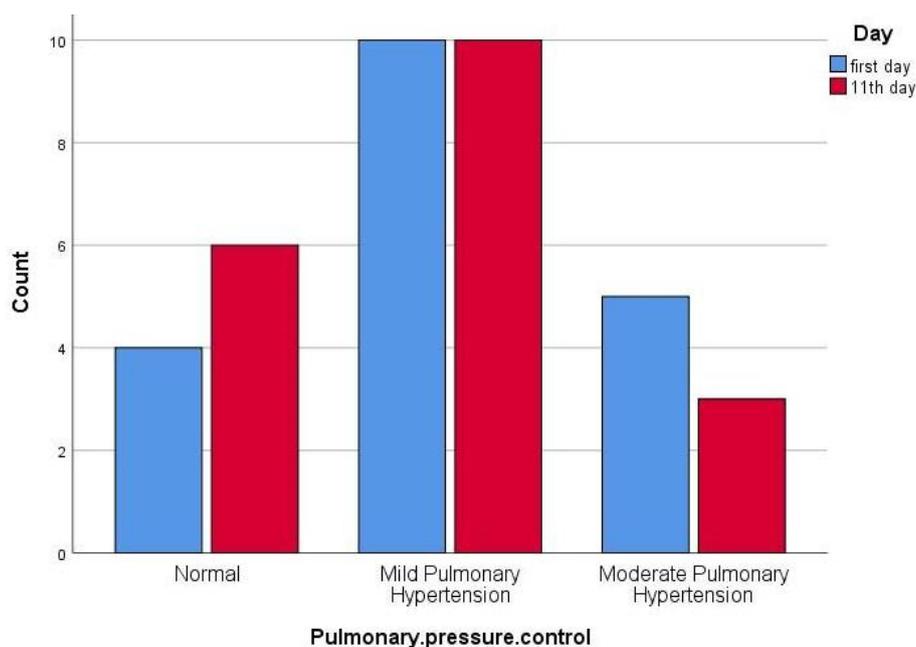
Characteristics		Group		P-value
		Intervention	Control	
Sex, n (%)	Male	7 (36.8)	9 (47.4)	
	Female	12 (63.2)	10 (52.6)	
Pulmonary pressure of the first day, n (%)	normal	2 (10.5)	4 (21.1)	0.607**
	Mild	10 (52.6)	10 (52.6)	
	Medium	7 (36.8)	5 (26.3)	
	Severe	0 (0.0)	0 (0.0)	
Pulmonary pressure after the end of treatment, n (%)	Normal	13 (68.4)	6 (31.6)	0.069**
	Medium	4 (21.1)	10 (52.6)	
	Severe	0 (0.0)	0 (0.0)	
Improvement pulmonary pressure, n (%)		13 (68.4)	4 (21.1)	0.003*

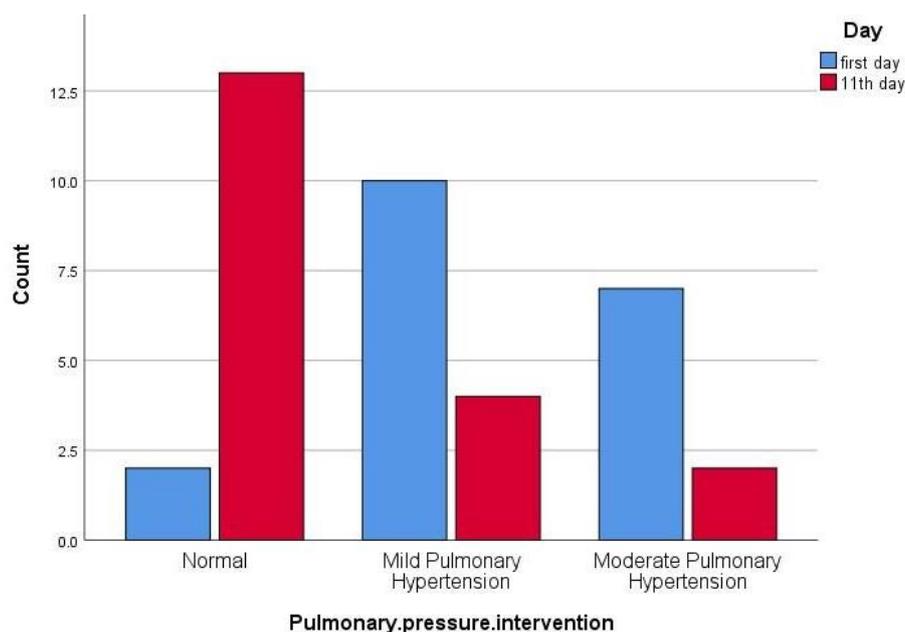
**Table-2:** The patients' conditions and recovery process during hospitalization

Characteristic	Groups		P-value
	Intervention	Control	
Age of starting treatment (day)	29.47 ( $\pm$ 2.14)	29.47 ( $\pm$ 0.84)	0.212*
Gestational age of birth (week)	28.32 ( $\pm$ 1.66)	26.68 ( $\pm$ 1.25)	0.479*
Duration of hospitalization after starting treatment (day)	21.00 ( $\pm$ 9.36)	35.26 ( $\pm$ 13.55)	0.006*
Duration of reaching of fiO2 to 21%	8.42 ( $\pm$ 3.92)	8.11 ( $\pm$ 8.38)	0.400*
Duration of start of respiratory support as oxygen free flow	8.21 ( $\pm$ 3.84)	11.47 ( $\pm$ 9.19)	0.001*
<b>Duration of discontinuation of respiratory support FIO2</b>	16.21 ( $\pm$ 5.89)	22.95 ( $\pm$ 6.51)	0.003*
FiO2 of the first day	38.53 ( $\pm$ 14.68)	29.11 ( $\pm$ 11.92)	
FiO2 of the end of treatment	22.22 ( $\pm$ 2.98)	26.48 ( $\pm$ 9.47)	
P-value within group	0.001**	0.037**	
<b>Systolic blood pressure</b>			
Systolic blood pressure of the first day	71.32 ( $\pm$ 5.48)	61.32 ( $\pm$ 4.36)	
Systolic blood pressure after the end of treatment	57.63 ( $\pm$ 4.82)	57.74 ( $\pm$ 4.24)	
P-value within group	0.001**	0.001**	
<b>Diastolic blood pressure</b>			
Diastolic blood pressure of the first day	51.84 ( $\pm$ 4.15)	44.21 ( $\pm$ 3.82)	
Diastolic blood pressure after the end of treatment	42.37 ( $\pm$ 3.86)	40.00 ( $\pm$ 3.33)	
P-value within group	0.001**	0.001**	
<b>Heart rate</b>			
Heart rate of the first day	136.32 ( $\pm$ 8.47)	133.84 ( $\pm$ 8.64)	
Heart rate after the end of treatment	129.79 ( $\pm$ 5.62)	134.79 ( $\pm$ 9.57)	
P-value within group	0.029**	0.777**	

\*P-value by independent sample t-test

\*\*P-value by pair sample t-test

**Fig. 1:** The pulmonary pressure changes in the control group



**Fig. 2:** The pulmonary pressure changes in the intervention group

#### 4- DISCUSSION

Because of some evidences of the positive effects of sildenafil on controlling and treating the chronic lung disease in infants and also because of controversial findings on the side effects of sildenafil in previous studies, this study aimed to investigate the role of sildenafil in the treatment of chronic lung disease in infants.

The results of the present study showed that sildenafil significantly reduced the duration of admission, and need for respiratory support as well as reducing oxygen administration and pulmonary pressure. On the other hand, the results of the present study showed that treatment with sildenafil had no significant effect on the rate of changes in  $FiO_2$ , the timeline for reaching  $FiO_2$  level to 21% and the patients' heart rate, but it reduced further systolic and diastolic blood pressure. However, no severe systolic or diastolic blood pressure was observed in any of the patients and this reduction in systolic and diastolic pressure was not clinically significant.

The findings of the present study were in line with previous studies. In a study by Mourani et al. on 25 infants with PPHN and chronic lung disease, the results showed that chronic treatment with sildenafil (mean treatment duration of 40 days) improved hemodynamics in 22 patients (88%). In these patients, the ratio of pulmonary artery pressure to systemic systolic pressure decreased by at least 20%. Out of 25 patients, 5 patients died during follow-up and treatment with sildenafil in 2 patients was stopped due to side effects (recurrent erection and NEC) (15). However, in the present study, these side effects (recurrent erection and NEC) were not observed.

Khorana et al., In a study on 11 infants diagnosed with PPHN, showed that the oxygenation index progressively decreased after the addition of sildenafil to supportive therapies (16). In the present study, although sildenafil had little effect on  $FiO_2$ , in line with the study by Khorana et al., it reduced the need for respiratory support. In the study by Khorana et al., sildenafil was discontinued on one patient due to hypotension, and one patient died during treatment. This study identifies

systemic hypotension as the most important challenge of sildenafil use. However, in the present study, despite a relative decrease in systolic and diastolic pressure, no cases of systemic hypotension were observed.

In a study by Sayed et al., on 27 patients diagnosed with PPHN, the effects of sildenafil treatment were evaluated. Clinical response to sildenafil was observed in 78% of patients. Decreased oxygenation index, increased arterial oxygen pressure and decreased  $FiO_2$  occurred significantly in patients. However, this treatment was not effective in 6 patients and one of them died due to sepsis. None of the patients experienced significant hypotension (17). In contrast to this study, in the present study, sildenafil had no significant effect on  $FiO_2$ . This may be due to the significant difference in  $FiO_2$  levels between the two groups at the time of enrollment. Despite the random grouping of patients, the mean  $FiO_2$  in the intervention group was significantly higher than the control group and the effect of sildenafil in these patients may not be able to show the rates of changes in  $FiO_2$ .

Kadmon et al., reviewed the medical records of 25 infants with PH-related BPD at the Pediatric Pulmonary Hypertension Clinic between 2008 and 2014, and similar to the findings of the present study, they showed that treatment for BPD in which the patient's condition was exacerbated by pulmonary hypertension (PH), PH-specific drugs, mainly sildenafil, were associated with improved clinical and hemodynamic parameters and low mortality (18).

Nyp et al. designed a study to determine the effects of sildenafil citrate on gas exchange in neonates with bronchopulmonary dysplasia (BPD) related to PH. Sildenafil citrate was used for 21 preterm infants with BPD-related PH. Similar to the present study, it was

reported that a significant reduction in right ventricular systolic pressure was observed after the start of sildenafil citrate administration. Seven infants showed a more than 20% reduction in right ventricular peak systolic pressures (19).

Wardle et al. examined whether sildenafil alone or in combination with other known therapeutic agents is effective in improving the pediatric PH with BPD or not. This study similarly to the present study showed that sildenafil in the treatment of this disease is safe and also effective. The study also showed that if continued during the PH impairment period, the drug could improve survival from 61% to 81% in 12 months (20).

Herbert et al., in another study provided evidence that if consuming that drug continued until complete PH recovery, mortality in patients with BPD might be reduced. Treatment with sildenafil at a maximum dose of 2 mg/kg every 6 hours can be considered in neonates with PH-BPD. It seems that this drug has positive hemodynamic benefits, a safe and appropriate profile, and the use of this drug is recommended in combination with other treatments. However, the author reported that because of the lack of evidence for an unbiased approach and possible accurate mortality data in other articles, prescribing should be limited to specialist units and physicians, ideally experienced in dealing with BPD and PH, and in other cases treatment options are limited (21).

In another study, Park et al., studied sildenafil clinically to improve the pulmonary function in patients with BPD. Based on the pharmacological action of sildenafil, an increase in cyclic guanosine 3', 5'-monophosphate (cGMP) in lung tissue has been suggested as a precursor to beneficial effects, but this mechanism is not well understood at the molecular level. Here, the Author explored the possibility

that sildenafil helped the pulmonary system to adapt to hyperoxic stress.

The most common side effects of sildenafil are nausea and vomiting, abdominal pain, and coughing; however, migraines and sleep disturbances can also be provoked. It is noteworthy that Vi-PDE has previously been associated with retinal dysfunction, however, an 8-month evaluation has shown no evidence of this, although discontinuation in the development of visual impairment and contraindication to sildenafil in patients with inherited retinal damage or hearing are recommended (23). In a study on 43 patients with PH-BPD, only two disorders were reported that led to discontinuation of the drug. The systemic hypotension was observed in an infant at a dose of 0.5 mg/kg/day; but after 3 days of contraindication this dose is tolerated and can be titrated to 4 mg/kg/day (24). Although a decrease in systolic and diastolic blood pressure was observed in our study, no cases of hypotension or other side effects of sildenafil were found among the neonates in the present study.

#### Limitations of the study

Low sample size and study on neonates in one setting are the main limitations of this study. It is, thus, suggested that this study be performed in a multi-center manner with a wider number of patients for more reliable documentation. It is also suggested that in future studies, these patients be followed up for medium and long-term outcomes.

#### 5- CONCLUSION

The results of the present study showed that sildenafil significantly reduced the duration of hospitalization, and need for respiratory support. Moreover, it led to a significant reduction in oxygen administration and pulmonary pressure. Also, no specific side effects of sildenafil were found in this study. Therefore, sildenafil can be considered as

a safe and effective drug in infants with chronic lung diseases.

#### 6- CONFLICT OF INTEREST

None.

#### 7- ACKNOWLEDGEMENTS

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#### 8- AUTHORS' CONTRIBUTIONS

M. Mussavi designed the first concept and helped with the first draft and critical revision of the manuscript. Shahram Sadeghvand analyzed and interpreted the data, participated in the manuscript preparation and critical revision. All authors read and approved the final version of the manuscript.

#### 9- REFERENCES

1. Chen YH, Song Y, Yu YL, Cheng W, Tong X, miRNA-10a promotes cancer cell proliferation in oral squamous cell carcinoma by upregulating GLUT1 and promoting glucose metabolism. 2019. 17(6): p. 5441-5446.
2. Steinhorn RH, Kinsella JP, Pierce C, Butrous G, Dilleen M, Oakes M, Wessel DL, Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. 2009. 155(6): p. 841-847. e1.
3. Donn, S.M. and S.K. Sinha, Manual of neonatal respiratory care. 2012: Springer.
4. Jensen, E.A., B.J.B.D.R.P.A.C. Schmidt, and M. Teratology, Epidemiology of bronchopulmonary dysplasia. 2014. 100(3): p. 145-157.
5. Collins JJP, Tibboel D, Kler IMD, Reiss IKM, Rottier RJ, The future of bronchopulmonary dysplasia: emerging pathophysiological concepts and potential new avenues of treatment. 2017. 4: p. 61.

6. Malavolti AM, Bassler D, Arlettaz-Mieth R, Faldella G, Latal B, Natalucci G, Bronchopulmonary dysplasia—impact of severity and timing of diagnosis on neurodevelopment of preterm infants: a retrospective cohort study. 2018. 2(1).
7. Maria MVD, Younoszai AK, Mertens L, Landeck BF, Ivy DD, Hunter KS, Friedberg MK, RV stroke work in children with pulmonary arterial hypertension: estimation based on invasive haemodynamic assessment and correlation with outcomes. 2014. 100(17): p. 1342-1347.
8. König K, Barfield CP, Guy KJ, Drew SM, Andersen CC, The effect of sildenafil on evolving bronchopulmonary dysplasia in extremely preterm infants: a randomized controlled pilot study. 2014. 27(5): p. 439-444.
9. Papoff P, Cerasaro C, Caresta E, Barbàra CS, Midulla F, Moretti C, Current strategies for treating infants with severe bronchopulmonary dysplasia. 2012. 25(sup3): p. 15-20.
10. Greenough, A. Long term respiratory outcomes of very premature birth (< 32 weeks). In *Seminars in Fetal and Neonatal Medicine*. 2012. Elsevier.
11. Gough A, Spence D, Linden M, Halliday HL, McGarvey LPA, General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia: a systematic review. 2012. 141(6): p. 1554-1567.
12. Anderson, P.J. and L.W. Doyle. Neurodevelopmental outcome of bronchopulmonary dysplasia. In *Seminars in perinatology*. 2006. Elsevier.
13. Simonca, L. and R.J.C. Tulloh, Sildenafil in infants and children. 2017. 4(7): p. 60.
14. Ladha F, Bonnet S, Eaton F, Hashimoto K, Korbitt G, Thébaud B, Sildenafil improves alveolar growth and pulmonary hypertension in hyperoxia-induced lung injury. 2005. 172(6): p. 750-756.
15. Mourani PM, Sontag MK, Ivy DD, Abman SH, Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. 2009. 154(3): p. 379-384. e2.
16. Khorana M, Yookaseam T, Layangool T, Kanjanapattanakul W, Paradeevisut H, Outcome of oral sildenafil therapy on persistent pulmonary hypertension of the newborn at Queen Sirikit National Institute of Child Health. 2011. 94: p. S64-73.
17. Sayed, A. and N.J.J.o.n.-p.m. Bisheer, Outcome of oral sildenafil in neonatal persistent pulmonary hypertension of non-cardiac causes. 2015. 8(3): p. 215-220.
18. Kadmon G, Schiller O, Dagan T, Bruckheimer E, Birk E, Schonfeld T, Pulmonary hypertension specific treatment in infants with bronchopulmonary dysplasia. 2017. 52(1): p. 77-83.
19. Nyp M, Sandritter T, Poppinga N, Simon C, Truog WE, Sildenafil citrate, bronchopulmonary dysplasia and disordered pulmonary gas exchange: any benefits? 2012. 32(1): p. 64-69.
20. Wardle AJ, Wardle R, Luyt K, Tulloh R, The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. 2013. 98(8): p. 613-617.
21. Herbert, S. and R.J.E.h.d. Tulloh, Sildenafil, pulmonary hypertension and bronchopulmonary dysplasia. 2016. 102: p. 21-24.
22. Park HS, Park JW, Kim HJ, Choi CW, Lee HJ, Kim BI, Chun WS, Sildenafil alleviates bronchopulmonary dysplasia in neonatal rats by activating the hypoxia-inducible factor signaling pathway. 2013. 48(1): p. 105-113.

23. Cordell WH, Maturi RK, Costigan TM, Marmor MF, Weleber RG, Coupland SG, Danis RP, McGettigan JR, Antoszyk AN, Klise S, Sides GD, ERG Testing During Chronic PDE5 Inhibitor Administration (ERG-PDE5i) Consortium, Retinal effects of 6 months of daily use of tadalafil or sildenafil. 2009. 127(4): p. 367-373.
24. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, Sastry BKS, Pulido T, Layton GR, Serdarevic-Pehar M, Wessel DL, A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. 2012. 125(2): p. 324-334.