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Original Research

If We Cannot Use Nitric Oxide for Newborn Persistent Pulmonary Hypertension, is Oral Sildenafil Therapeutic? A Single-center Experience

Selçuk Gürel[1,*]

[1]Department of Pediatrics, NICU, Öztan Hospital, 64200 Uşak, Turkey
*Correspondence: gurelselcuk@gmail.com (Selçuk Gürel)
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Abstract

Background: Persistent pulmonary hypertension is still an issue in newborn period with different treatment strategies. In this study, we aimed to evaluate the three-year experience of a neonatal intensive care unit on use of sildenafil citrate for treating newborns with persistent pulmonary hypertension. **Methods**: Twenty-nine newborn patients with the diagnosis of persistent pulmonary hypertension solely treated by sildenafil citrate (2 mg/kg per dose, orally, three times a day) in intensive care unit of a private hospital between 2018 and 2021 were retrospectively analyzed. **Results**: The newborns that underwent sildenafil treatment and the newborns that received no treatment had statistically similar length of hospital stay ($p = 0.188$). The premature newborns had significantly lower systolic and diastolic blood pressure than the term newborns on their first day of sildenafil treatment ($p = 0.001$ for both). The premature newborns had significantly lower systolic, diastolic, and right ventricular systolic pressure than the term newborns on their day of hospital discharge ($p = 0.003$, $p = 0.013$ and $p = 0.001$ respectively). The premature newborns had significantly lower systolic, diastolic, and right ventricular systolic pressure on their day of hospital discharge than their first day of sildenafil treatment ($p = 0.039$, $p = 0.041$ and $p = 0.043$ respectively). The term newborns had also significantly lower systolic, diastolic, and right ventricular systolic pressure on their day of hospital discharge than their first day of sildenafil treatment ($p = 0.001$ for each). **Conclusions**: Sildenafil citrate can be considered as an efficient and safe alternative for the treatment of persistent pulmonary hypertension in newborn at the in tertiary neonatal intensive care units without nitric oxide and devices.

Keywords: hypertension; pulmonary; infant; low birth weight; intensive care units; neonatal; sildenafil citrate

1. Introduction

Pulmonary hypertension (PHT) is a significant cardiovascular condition marked by higher mean pulmonary arterial pressure (mPAP) and extended right ventricular afterload exposure. Persistent pulmonary hypertension of the newborn (PPHN) results due to circulatory adaptation failure following birth [1]. PHT is virtually invariably caused by pulmonary vascular resistance (PVR) dysfunction in neonates It is characterized by persistent elevation of pulmonary vascular resistance in presence of normal or low systemic vascular resistance [2]. The syndrome induces right-to-left extrapulmonary shunting which results in chronic pulmonary disease, asphyxia, neurodevelopmental sequels, and death [1,2].

PPHN is related with a variety of cardiopulmonary diseases, with a prevalence ranging from 0.4–6.8 per 1000 live births in low-risk neonates and 5.4 per 1000 live births in high-risk neonates. The overall mortality rate for neonates with PPHN was 7.6 percent, with a 10.7 percent mortality rate for babies with severe PPHN. Surviving PPHN newborns have a greater risk of long-term morbidity, such as a 25% neurodevelopmental impairment at two years [3]. The pathophysiology depends on delay and/or impairment in pulmonary vasculature relaxation [4]. One of the most important events in its pathogenesis is the decrease in cyclic guanosine monophosphate (cGMP) secondary to hypoxia and the increase in thromboxane and endothelin synthesis, resulting in the release of calcium, contraction of pulmonary smooth muscle and proliferation of vascular smooth muscle [5]. Other pathways in pathophysiology are caused by nitric oxide pathway, prostacyclin–adenosine monophosphate pathway, Rho-A/Rho-Kinas (ROK) pathway, endothelin pathway and free radicals [6]. Term neonates with hypoxemic respiratory failure are frequently assumed to be due to PPHN physiology; however, many hypoxemic newborns do not have extrapulmonary shunting across the Patent ductus arteriosus (PDA) or patent foramen ovale (PFO) on echocardiography. PPHN refers to babies who are hypoxemic and have signs of extrapulmonary shunting [3]. This frequently causes bronchopulmonary dysplasia, respiratory distress syndrome, congenital diaphragmatic hernia, and meconium aspiration syndrome [1,4].

Murmur, cyanosis, prolonged capillary filling time, metabolic acidosis in blood gas, and a rise in lactate level are all identified during the diagnosis. In PPHN, the preductal (right arm) oxygen saturation level is found to be

greater than 5% postductal (from the leg) and the difference between preductal and postductal partial oxygen pressure (PaO2) levels is at least 15 mmHg when measured using a pulse oximeter device. However, if there is a large shunt at the level of the foramen ovale, this difference may not exist. On an electrocardiogram (ECG), ST elevation can be noticed, although its diagnostic value is limited. Unless there is an underlying ailment, partial carbon dioxide pressure (pCO2) is normally normal [5]. The hyperoxia test is used to differentiate between circulatory and parenchymal disorders of the lungs [1]. Echocardiography (ECHO) is the gold standard for excluding structural abnormalities when diagnosing PPHN. Enlarged right ventricle and compressed left ventricular ECHO identify high PVR, reduced pulmonary blood flow, right and left ventricular function disorder, and inadequate systemic blood flow [3].

Treatment of hypothermia, hypoglycemia, anemia, and/or hypovolemia in neonates with PPHN should include sepsis assessment, rectification of metabolic acidosis, and regular monitoring of pulse oximetry, arterial blood pressure (pre- and post-ductal), and transcutaneous pCO2. It's also crucial to enhance cardiac output and systemic oxygen transport by optimizing systemic hemodynamics with volume and cardiotonic treatment. Extracorporeal membrane oxygenation is used to treat newborns who do not respond to medical therapy, as shown by a failure to maintain improvements in oxygenation with appropriate hemodynamic function. If antibiotics or a surfactant are required, they should be administered as quickly as possible [7]. In infants with PPHN, the safest and most suitable treatment measures appear to be avoidance of both hypoxia and hyperoxia, as well as preservation of oxygen levels within physiologically normal ranges (PaO2 ranges between 60 and 100 mmHg) [6].

Inhaled nitric oxide (iNO) has been the baseline treatment since 1999 when it was approved [8]. Despite the fact that it generates powerful and selective pulmonary vasodilation without lowering systemic vascular resistance, the success rate is around 40% [9]. Moreover, it is contraindicated in newborns with congenital heart diseases causing right-to-left shunting [10]. The risk of pulmonary edema is increased in patients with pre-existing left ventricular dysfunction and there is always risk for rebound pulmonary hypertension following cessation [9,10].

Sildenafil decreases pulmonary vascular resistance by blocking Phosphodiesterase 5 (FDE5), which inhibits cGMP from being degraded and converted to guonosine monophosphate [11]. Previous research has demonstrated that giving sildenafil to babies when NO is present lowers pulmonary vascular resistance and lowers mortality without causing clinically significant adverse effects. After starting oral medication, maximum serum levels are attained 0.5–2 hours later. The cytochrome p450 enzyme in the liver breaks it down. Sildenafil, which has a four-hour elimination half-life, is excreted 13 percent in the urine and 80 percent in the feces. Sildenafil citrate inhibits phosphodiesterase type 5 (PDE 5) [12] and it has been approved only in adult pulmonary hypertension. The primary circulating metabolite, N-desmethyl sildenafil, has an *in vitro* potency of 50% that of the parent molecule [13]. It effectively improves oxygenation and reduces mortality in PPHN [14,15].

In this study, we aimed to evaluate the three-year experience in neonatal intensive care unit of a private hospital on sildenafil citrate treatment of PPHN and to show that oral sildenafil is therapeutic if we cannot use NO in neonatal persistent pulmonary hypertension.

2. Materials and Methods

The study is a retrospective cohort study comprising 29 patients diagnosed with PPHN treated with sildenafil citrate (2 mg/kg per dose, orally, three times a day) at the intensive care unit of a private hospital between 2018 and 2021. The sildenafil therapy was continued till discharge in every patient.

Techniques for measuring pulmonary vascular resistance, myocardial function and blood flow in a sick baby, such as cardiac catheterization and MRI, are currently unavailable. Despite starting RDS and lung treatment in 29 of our patients, all patients who continued to need oxygen were intubated with a mechanical ventilator. Oxygen saturation was between 65–70% and preductal (right arm) oxygen saturation level was higher than 10% postductal (leg) and the difference between preductal and postductal partial oxygen pressure (PaO2) levels was 15 mmHg was more than. Hypoxia was also observed in blood gas follow-ups. Echocardiography, which is commonly used to confirm the diagnosis of PPHN and assess disease progression or therapy response, is the only relevant bedside clinical study now. It is a simple, noninvasive bedside test that may be performed on even the most unconscious patients [6]. The diagnosis was made by the consultant pediatric cardiologist, depending on the existence of two echocardiography criteria [16]: (i) Right-to-left or bidirectional hemodynamic shunting at the ductus arteriosus or at patent foramen ovale, (ii) Tricuspid regurgitation jet pressure >40 mmHg. Pulmonary artery pressure (PAP) was measured by adding this jet to right atrial pressure. It is normally 5 to 10 mmHg in newborns [17].

The newborns with congenital heart diseases, the newborns with other congenital anomalies, the newborns with chromosomal abnormalities, the newborns with active seizures and the newborns with pneumothorax were excluded from the study. All the newborns treated at the intensive care unit were discharged when they were clinically stable and were able to be fed orally. Since ECMO treatment can be performed in rare centers in the neonatal period, information about newborn transfer was available in our clinic and emergency aid and transfer centers when needed.

The present study was approved by the Institutional Review Board and Ethical Committee and written informed consent was obtained from the parents of the newborns at admission. No adverse effects related with sildenafil use occurred during the study period. Data related with gestational age at the time of delivery, birth weight, length of hospital stay, and blood pressures were acquired from hospital records.

The degree of PPHN was designated as mild, moderate, and severe according to the right ventricular systolic pressure estimated by the echocardiographic indices including tricuspid regurgitation jet, septal position, and left ventricular systolic circular index. Severe PPHN was diagnosed when right ventricle systolic pressure exceeded 2/3 of systemic pressure. Moderate PPHN was identified when right ventricle systolic pressure corresponded to 1/2 to 2/3 of systemic pressure and mild PPHN when right ventricle systolic pressure correlated to 1/3 to 1/2 of systemic pressure. Right ventricle systolic pressure less than 1/3 of systemic pressure was designated as normal. In addition, ECHO, saturation, and preductal-post ductal pressure measurements were used to monitor the severity of PPHN.

2.1 Echocardiographic Examination

Within 24 hours after their arrival, all neonates hospitalized to the research center's critical care unit completed a screening echocardiography assessment. A standardized cross-sectional and Doppler echocardiographic examination was done using 6-MHz transducers and various orthogonal parasternal, suprasternal, apical, and subcostal views (Vivid S6, GE Healthcare, UK). As for the newborns receiving sildenafil citrate, echocardiography examination was repeated at their first day of treatment and the day of hospital discharge. Using continuous wave Doppler echocardiography, TR jet regurgitation was obtained from the view that afforded the best alignment with regurgitant flow.

2.2 Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 22.0 (SPSS IBM, Armonk, NY, USA). Continuous data were expressed as mean $\pm$ standard deviation. The normality of data distribution was assessed by Kolmogorov-Smirnov test and statistical comparisons were made by means of Student *t*-test, Wilcoxon test and Mann Whitney U test. In order to avoid Type 1 errors by multiple comparisons, *post hoc* method was used to adjust alpha levels according to the number of subgroups. Two-tailed p values less than 0.05 were accepted to be statistically significant.

3. Results

During the study period, 389 newborns; 225 premature (57.8%) and 164 term (42.2%) were admitted to the intensive care unit of the study center. The rate of PPHN was 7.5% (29 patients) in this cohort of which 5 with PPHN (17.2%) were premature. Four newborns (13.8%) had severe, 13 newborns (44.8%) had moderate, and 12 newborns (41.4%) had mild PPHN.

In Table 1, the birth weight of premature and mature infants who received and did not receive treatment, the number of days they stayed in the intensive care unit, and the mean and standard deviations of the week of gestation are given. The descriptive statistics and statistical comparison of the babies who received and did not receive treatment in terms of the number of days spent in the intensive care unit are given in Table 2. Although the number of days in the intensive care unit was shorter in both premature and mature infants who did not receive treatment, there was a statistically significant difference in mature infants ($p < 0.05$).

Table 3 presents comparisons for systolic blood pressure, diastolic blood pressure, and RVSP (Right ventricular systolic pressure) values of 29 infants in the treatment group at the start of treatment and at discharge. Statistically significant decreases were recorded at the end of treatment for all three variables ($p < 0.0001$). In particular, RVSP values decreased by half. The graph of the changes at the beginning and end of the treatment is given in Fig. 1.

For the three variables examined in Table 4, both the initiation and end of treatment comparisons of premature and mature infants, as well as the comparisons of premature and mature infants at the beginning and end of treatment are shown. The mean systolic blood pressure, which was 60.40 at the beginning of the treatment in premature babies, decreased to an average of 38.00 at the end of the treatment, showing a statistically significant decrease ($p < 0.05$). Similarly, systolic blood pressure, which was 78.13 in mature babies, decreased to 56.96, showing a statistically significant decrease ($p < 0.001$). However, the difference between the systolic blood pressures of premature and mature babies was found to be statistically significantly different both at the beginning and at the end of the treatment ($p < 0.01$).

While RVSP was 36.20 in premature babies at the beginning of the treatment, it decreased by half to an average of 18.00 at the end of the treatment ($p < 0.05$). A similar decrease was also observed in mature infants ($p < 0.001$). The statistical significance of the decrease in mature babies can be explained by the small sample size in premature babies. There was no statistically significant difference between the mean RVSP value of 46.00 in mature babies at the beginning of the treatment and the mean of premature babies ($p > 0.05$). However, at the end of the treatment, the mean value of 18.00 in premature babies was found to be statistically significantly lower than the value of 23.00 in mature babies. Premature babies had lower systolic blood pressures on average. Similar results were obtained for diastolic blood pressure.

Table 1. Descriptive statistics for treatment and non-treatment groups.

		Birth weight	Week in gestation	Day in intensive care
Non Treatment	Preamature (n = 220)	1770.95 ± 556.63	31.38 ± 2.73	28.00 ± 19.53
	Mature (n = 140)	3019.39 ± 590.54	37.79 ± 1.66	10.16 ± 4.00
	Total (n = 360)	2256.46 ± 833.95	33.87 ± 3.93	21.06 ± 17.74
Treatment	Preamature (n = 5)	1722.00 ± 635.78	30.40 ± 4.04	33.40 ± 16.96
	Mature (n = 24)	3139.38 ± 750.89	38.04 ± 1.57	12.63 ± 4.08
	Total (n = 29)	2895.00 ± 904.31	36.72 ± 3.60	16.21 ± 10.89
	General (n = 389)	2304.72 ± 854.66	34.07 ± 3.96	20.53 ± 17.38

Table 2. Comparison of treatment and non-treatment groups in terms of number of days in intensive care unit within weeks.

	Non treatment			Treatment			
Weeks	Mean ± S.D.[a]	Median (MAD[b])	Min.–Max.	Mean ± S.D.[a]	Median (MAD[b])	Min.–Max.	*p* value
Premature	28 ± 19.53	22 (11)	1–95	33.4 ± 16.96	30 (8)	16–60	0.307
Mature	10.16 ± 4	11 (2)	1–26	12.63 ± 4.08	11 (1)	8–24	0.027

Note: (a) S.D., Standart Deviation; (b) MAD, Median absolute deviation.

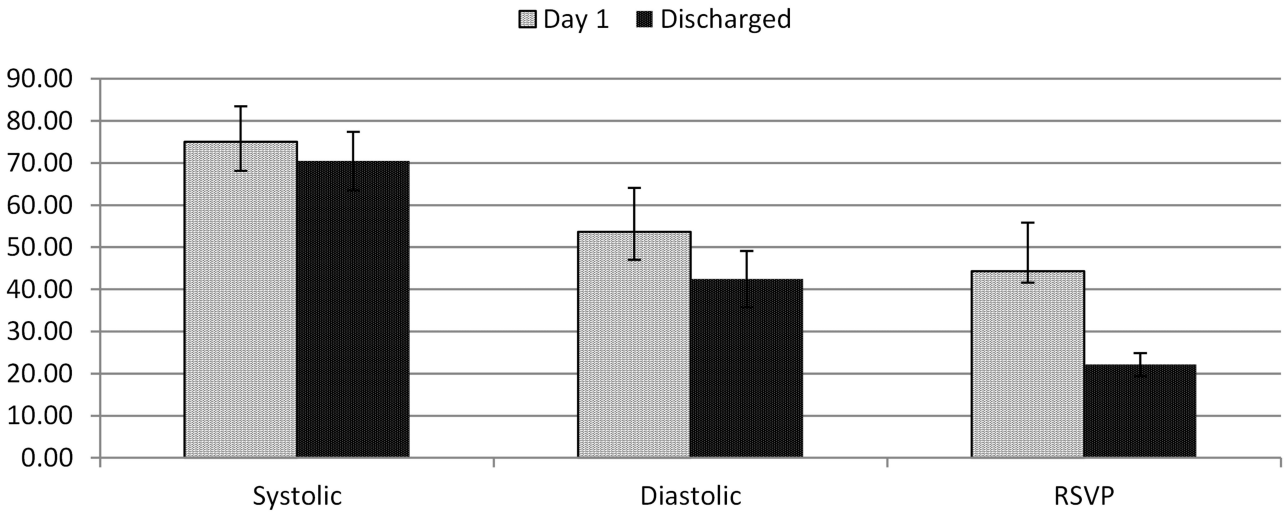

Fig. 1. Comparison of Day 1 and Discharged for variables in sildenafil group.

When the infants who received and did not receive inotropic agents (dopamine and dobutamine) both at the beginning and at the end of the treatment were compared, no statistically significant difference was found in any of the three variables examined ($p > 0.05$). The results are given in Table 5. On the other hand, changes at the end of treatment and at the end of treatment were statistically significant in both groups. The higher p values in infants receiving inotropes can be explained by the low sample size.

4. Discussion

Labile hypoxemia is a common observation in babies with PPHN, as is a difference in oxygen saturations more than 10% between pre-ductal (right upper extremity) and post-ductal (left upper extremity) values. A pre- and post-ductal oxygen saturation gradient of more than 10% shows the presence of extrapulmonary right-to-left shunting at the DA [18]. We observed a difference of more than 10% in the blood pressure measurements we made in all our PPHN patients before the ECHO. Pneumovascular oligemia, normal or moderate hyperinflation, and a lack of parenchymal infiltrates are common radiographic findings in idiopathic PPHN [3]. All our patients had these findings in their PA chest radiographs. The pulmonary adaptation in newborn period following birth refers to pulmonary vascular resistance decrease and a prominent pulmonary blood flow increase [2]. Increased partial oxygen pressure, pulmonary parenchyma distension, pulmonary secretion drainage increase, and vasoactive mediator synthesis increase are the major factors that enhance pulmonary vasodilatation thus, pulmonary vascular resistance reduction [1,3]. These factors affect through endothelial nitric oxide synthase (ENOS) activation [3]. The activation of ENOS accelerates the production of nitric oxide halving pulmonary vascular resistance [4,8].

Table 3. Comparison of Day 1 and Discharged for variables in sildenafil group.

		Descriptive Statistics					Paired *t* test		Post hoc power of test	
		N	Mean	S.D.	Min.	Max.	*t*	*p* value	Effect size	Power
Systolic	Day 1	29	75.07	8.41	52.00	86.00	5.815	<0.0001	1.504	1.000
	Discharged	29	70.48	6.94	48.00	82.00				
Dystolic	Day 1	29	53.69	10.43	24.00	68.00	7.494	<0.0001	1.437	1.000
	Discharged	29	42.45	6.70	28.00	54.00				
Rvsp	Day 1	29	44.31	11.50	25.00	72.00	11.482	<0.0001	2.102	1.000
	Discharged	29	22.14	2.72	16.00	26.00				

Note: S.D., Standart Deviation.

Table 4. Clinical features of the newborns on sildenafil treatment with respect to maturity.

		Day 1		Discharged		*p* value[c]	Post hoc power
	Week	Mean ± S.D.[a]	Median (MAD[b])	Mean ± S.D.[a]	Median (MAD[b])		
Systolic	Premature (n = 5)	60.40 ± 6.39	62.0 (6.0)	38.00 ± 11.83	38.0 (6.0)	0.039	0.953
	Mature (n = 24)	78.13 ± 4.75	78.0 (3.5)	56.96 ± 6.59	57.0 (5.0)	<0.001	1.000
	p value[d]	<0.001		0.003			
	Post hoc power	0.999		0.985			
Diastolic	Premature (n = 5)	59.20 ± 7.29	60.0 (2.0)	35.20 ± 6.10	34.0 (4.0)	0.041	1.000
	Mature (n = 24)	72.83 ± 4.00	72.0 (2.0)	43.96 ± 5.86	44.0 (2.0)	<0.001	1.000
	p value[d]	<0.001		0.013			
	Post hoc power	0.993		0.882			
RVSP	Premature (n = 5)	36.20 ± 8.61		18.00 ± 2.00	18.0 (2.0)	0.043	0.910
	Mature (n = 24)	46.00 ± 11.44		23.00 ± 1.96	23.0 (1.0)	<0.001	0.921
	p value[d]	0.078		0.001			
	Post hoc power	0.457		0.997			

[a]S.D., Standart Deviation; [b]MAD, Median absolute deviation; [c]Wilcoxon *p* value, [d]Mann Withney U *p* value.

Phosphodiesterase 5 is an enzyme degrading cyclic Guanilate Mono Phosphate (cGMP) in smooth muscle cells and inhibiting vasodilatation induced by nitric oxide [14]. It is highly expressed in fetal lungs, therefore a key regulator of pulmonary perinatal circulation and limits the decrease in pulmonary vascular resistance [14,15]. The inhibition prolongs cGMP activity duration and results in the relaxation of the smooth muscles, so dilatation of the pulmonary vasculature [19]. It is frequently used for treatment of adult pulmonary hypertension [13]. It is demonstrated that sildenafil is as efficient and safe as iNO for achieving pulmonary vasodilatation in a pig model of pulmonary hypertension due to meconium aspiration [20]. Moreover, a Cochrane review documented efficacy and safety of sildenafil in this indication in term and near-term neonates [21]. Five studies were compared; sildenafil versus no treatment or placebo, sildenafil versus another pulmonary vasodilator and the combination of sildenafil and another pulmonary vasodilator versus placebo and another pulmonary vasodilator. The diagnosis was based on clinical evaluation with or without echocardiographic examination. In the study of Herrera *et al*. [22], in which they compared those who used sildenafil in addition to conventional treatment and those who did not use sildenafil, it was found that there was a significant increase in oxygen saturation in the infants using sildenafil compared to the group that did not receive it, and in the group that received sildenafil in the first 3 days compared to the group that did not receive it, in the airway pressure and in the number of days connected to the ventilator found a decrease.

In the present study the mortality rate was not assessed because no baby died. Three studies resulted in reduced mortality rate when compared to placebo. On contrary, none reported significant decrease in mortality when sildenafil was compared to iNO treatment or the sildenafil and iNO combination. The increase in oxygenation index and partial oxygen pressure after the first sildenafil dose indicated an insignificant improvement and no adverse events related with sildenafil use were noticed [21]. On the other hand, Pierce *et al*. [23] study by adding IV sildenafil to iNO found no difference between sildenafil and placebo. however, the duration of hospital stay was shorter in the group with sildenafil added. Vargas *et al*. [24] reported a significant improvement in physiological parameters and mortality rates starting from the first dose. In this study, while the mortality rate was 20% in the sildenafil group, it was reported as 54% in the control group. In their study, Uslu *et al*. [25], in which they compared the efficacy of intravenous $MgSO_4$ and oral sildenafil in neonatal PPHT, reported that the need for inotropes was less in those using sildenafil and

Table 5. Inotropic agent.

	Inotropic agent	Day 1		Discharged		*p* value	Post hoc power
		Mean ± S.D.	Median (MAD)	Mean ± S.D.	Median (MAD)		
Systolic	No (n = 25)	75.56 ± 8.47	77.0 (5.0)	53.92 ± 10.72	55.0 (7.0)	<0.001	1.000
	Available (n = 4)	72.00 ± 8.49	73.0 (6.0)	52.25 ± 9.6	56.0 (1.5)	0.034	0.991
	p value	0.445		0.775			
	Power	0.126		0.061			
Diastolic	No (n = 25)	70.48 ± 6.59	72.0 (2.0)	42.6 ± 6.95	44.0 (2.0)	<0.001	1.000
	Available (n = 4)	70.50 ± 10.12	71.0 (7.0)	41.5 ± 5.51	41.0 (4.0)	0.034	0.982
	p value	0.974		0.750			
	Power	0.050		0.060			
RSVP	No (n = 25)	45.00 ± 11.99	42.0 (8.0)	22.24 ± 2.47	22.0 (2.0)	<0.001	1.000
	Available (n = 4)	40.00 ± 7.48	39.0 (4.0)	21.5 ± 4.43	22.0 (3.0)	0.033	0.936
	p value	0.505		0.845			
	Power	0.141		0.065			

the duration of mechanical ventilation was shortened. In contrast to previous trials, Aliva *et al*. [26] discovered in a retrospective investigation of 147 newborns that mortality increased with increasing sildenafil dosage. The usage of sildenafil at very high dosages, which is distinct from our study and other similar trials, is the cause of the increased fatality rate.

In our study there were no recorded adverse effect due to sildenafil usage. Sildenafil use in infants with PPHN was assessed. Hypotension, patent ductus arteriosus with left-to-right shunting, total anomalous pulmonary venous return, pneumothorax, trisomy 21 associated hypotension and adrenal insufficiency were the adverse effects reported [27]. Visual, musculoskeletal, auditory, and vestibular disorders were the adverse effects related with PDE 5 inhibitors [28]. A randomized controlled pilot research sildenafil with nasogastric tube (4 doses per day from 2 mg/kg), like ours, found that newborns with PPHN had better oxygenation than placebo controls [29]. As in our study, oxygen saturation was enhanced by pulse oximetry without any decrease in blood pressure. Unlike in our study, examining heart pressure data with echocardiography yielded more objective favorable outcomes.

Despite sildenafil being the most used off-label oral medication for treatment of children with pulmonary hypertension, it is not approved by FDA in pediatric population [30–32]. Moreover, the recently published data from the sildenafil in previously non-treated children aged 1 to 17 years has documented that PPHN have raised controversy on safety and efficacy [32,33]. The most important limitation of the STARTS trials is the exclusion of infants younger than 1 year so that the utility of sildenafil citrate in this age group has remained a matter of debate [33,34]. This study was designed to contribute the knowledge on efficiency and safety of sildenafil citrate as the first line treatment by analyzing the experience of a tertiary health center. As we said in our study, earlier studies have shown that sildenafil medication may be beneficial in the treatment of babies with severe PPHN who do not react to iNO or who do not get iNO [3]. PPHN is a common newborn issue characterized by oxygenation failure, but it encompasses a wide range of physiologic factors that must be considered when making treatment decisions. For the best patient outcomes, early detection and good management are critical. We had severe, moderate, and mild patients in each of the three groups of patients who took part in the study. We did not, however, have any patients who exitus. This is the most significant distinction from past sildenafil research.

However, the power of the present study is limited by its small cohort and lack of simultaneous use of other pharmacological agents indicated. Currently available literature on this subject was limited since the quality of methodology was poor, scales were small, and data was inconsistent [21]. Despite the limitations, sildenafil is reported to be a promising choice [14]. Sildenafil use is especially preferred in PPHN patients who are resistant to iNO treatment, in whom iNO treatment is contraindicated and in case iNO is commercially unavailable [14,28].

5. Conclusions

As a result, the present study points out that sildenafil treatment does not prolong neonatal intensive care unit (NICU) stay. Besides, it significantly decreases systolic, diastolic blood pressure and right ventricular systolic pressure in both premature and term infants with PPHN. These findings imply that sildenafil citrate may be considered as an efficient and safe alternative for the treatment of PPHN in NICU. Further randomized trials are warranted to clarify the efficiency and safety of oral sildenafil citrate use in treatment of PPHN.

Author Contributions

SG study protocol development, recruitment, data collection, data analysis, final manuscript writing and review.

Ethics Approval and Consent to Participate

This clinical trial study protocol was approved by the approved by Uşak University Clinical Research Ethics Committee 23/05/2018 dated and numbered 68-7 and is in accordance with the guidelines laid by the Declaration of Helsinki. A written informed consent was obtained from all participants prior to their enrollment in this study.

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Conflict of Interest

The author declares no conflict of interest.

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