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Original Research

Effect of early adjunctive use of oral sildenafil and inhaled nitric oxide on the outcome of pulmonary hypertension in newborn infants. A feasibility study

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Abstract.
INTRODUCTION: Inhaled nitric oxide (iNO) is the standard therapy for infants with persistent pulmonary hypertension of the newborn (PPHN). Recently, sildenafil has been evaluated as an alternative or adjunctive pulmonary vasodilator.
OBJECTIVE: To assess the effectiveness of adding sildenafil as an early adjunctive therapy together with iNO when treating newborns with PPHN and/or hypoxemic respiratory failure.
METHODS: This is a randomized placebo trial on newborns with gestational age > 34 weeks, postnatal age < 48 hours, and diagnosed with PPHN (oxygen index (OI) $\geq$ 20). Newborns were randomized to two groups: Group A- received oral sildenafil and iNO, and group B- received placebo and iNO. Initial and follow up echocardiography were performed over 14 days period.
RESULTS: A total of 24 newborns were recruited; 13 of them received sildenafil in addition to iNO and 11 received iNO and placebo. The most common causes of PPHN were meconium aspiration syndrome, pneumonia, and RDS. At the starting point, OI was marginally higher in the intervention group without statistical significance (29 vs 28). There were no differences between the two groups regarding surfactant administration, incidence of pneumothoraces, and the underlying causes of PPHN. Sildenafil or placebo treatment started within 12 hours after starting iNO (8 vs 6 hours).
CONCLUSION: Early use of oral sildenafil next to iNO in cases of PPHN was tolerated well by newborns and it did not show significant adverse effects. Further studies with a larger sample size is needed to assess its effecacy.

Keywords: Newborn, pulmonary, hypertension, sildenafil, iNO, respiratory, oxygen index

Abbreviations

A-a ratio	alveolar arterial oxygen ratio
CLD	Chronic lung disease
ECMO	Extracorporeal membrane oxygenation

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HFOV	High frequency oscillatory ventilation
iNO	inhaled nitric oxide
IVH	Intraventricular hemorrhage
NICU	neonatal intensive care unit
OI	oxygen index
PAO2	alveolar oxygen
PaO2	arterial oxygen tension
PaCO2	Carbon di-oxide tension
PDA	Patent ductus arteriosus
PPHN	persistent pulmonary hypertension of newborn
ROP	retinopathy of prematurity
UAC	Umbilical arterial catheter
CMV	conventional mechanical ventilation

1. Introduction

Persistent pulmonary hypertension of the neonate [PPHN] is characterized by the hyper-reactivity of the muscle layer in pulmonary arterioles, which leads to increased pulmonary vascular resistance and pulmonary blood pressure with the consequent right-to-left shunt across the ductus arteriosus and foramen ovale in the absence of structural heart defects. PPHN can also include right ventricle dysfunction in many cases. The immediate outcome of this pathology is poor pulmonary blood flow and subsequent hypoxia [1]. The reported incidence rate is 0.43–6.8 per 1000 live newborn infants with a mortality of 10% to 20% [2]. The main objective of therapy in PPHN is to reduce pulmonary vascular resistance in order to improve the oxygenation of the body tissues. For this purpose, inhaled nitric oxide [iNO] has been a standard therapy [1, 3]. However, 30–40% of these infants do not respond to iNO therapy. Thus, other therapies have been tried with different success rates [4–6].

Recently, sildenafil has been evaluated as an alternative or adjunctive pulmonary vasodilator. It inhibits phosphodiesterase type 5 and elevates the concentration of cyclic guanosine monophosphate in the muscle cells of pulmonary vessels, which in turn decreases pulmonary vascular resistance [4, 7, 8]. In animal studies, sildenafil has been shown to overcome experimentally induced PPHN in lambs [9, 10]. In adult humans, these observations have also been confirmed [11]. However, although the European Medicines Agency produced a report in 2011 approving its pediatric use in Europe, the U.S. Food and Drug Administration recently issued a warning recommending against the off-label use of Revatio(r) (sildenafil) for children (aged 1-17) for the treatment of pulmonary artery hypertension (PAH) [12].

This review challenged the pediatric pulmonary community to assess the efficacy and safety of sildenafil further, especially when chronic treatment is needed. While low doses of sildenafil are likely to be safe for treating pediatric pulmonary hypertension, further studies should carefully examine its role in long-chronic pediatric patients with pulmonary hypertension who require close surveillance and frequent monitoring, and persistent sildenafil monotherapy is likely to be insufficient to prevent disease progression [13].

In some studies, sildenafil use has been postulated to be better than iNO [14]; there are also anecdotal reports of the benefits of sildenafil on infants with PPHN from centers where iNO is not available [15-18]. Furthermore, it could also decrease the risk of the rebound effect when iNO is discontinued [19]. Recently, three clinical trials compared sildenafil with placebos or controls in newborns with PPHN; one study evaluated 24 patients, the second evaluated 13 patients, while the third was a double-blind randomized clinical trial in 51 full-term infants with PPHN. All showed that sildenafil significantly improved the oxygenation index, decreased mortality, and reduced the risk of rebound after discontinuing iNO [20-22]. Similarly, the use of sildenafil to treat PPHN secondary to chronic lung disease in older infants has received significant attention over the past few years, with its tolerance and safety after long-term use reported to be safe [23–25].

Nevertheless, according to Cochrane [26], the safety and effectiveness of sildenafil in the treatment of PPHN has not yet been established and its use should be restricted within the context of randomized controlled trials. In addition, further randomized controlled trials of adequate power comparing sildenafil with other pulmonary vasodilators are needed in moderately ill infants with PPHN. Indeed, Cochrane's review in August 2011 recommended a large-scale randomized trial comparing sildenafil with the currently used vasodilator (i.e., iNO) to assess its efficacy and safety [26]. Such conclusions have not prevented practitioners from adding sildenafil as an off-label prescription adjunct to iNO when treating sick infants [27]. Moreover, popular pharmaceutical drug reference books such as the British National Formulary 2010 and Neofax 2009/2010 mention the drug doses for newborns in cases of PPHN.

In the women's hospital at Hamad Medical Corporation (HMC), the average number of deliveries is 15,000–17,000 per year with a 10% admission rate to NICU. The number of PPHN cases admitted to the NICU ranges between 14 and 20 cases every year. INO is the main and ultimate line of treatment for PPHN in the NICU in addition to using either CMV or HFOV. The international rate of response to iNO is 52% as a full response and 27% as a partial response, with a 21% failure rate [28].

The objective of this study is to evaluate the feasibility and effectiveness of adding sildenafil as an adjunctive therapy together with iNO when treating newborns with PPHN and/or hypoxemic respiratory failure and assess whether this approach could improve oxygenation, decrease the time on mechanical ventilation, and prevent rebound hypoxic episodes.

2. Methods

This is a feasibility study, design was a double-blinded placebo, prospective study. The study was conducted in the NICU of HMC in Doha, Qatar over a period of three years. Inclusion criteria were newborn infants of a postnatal age less than 48 hours; a gestation age equal to or more than 34 weeks; an oxygen index [OI] of more than or equal to 20 (moderately ill infants); radiological, clinical, and biochemical evidence of acute hypoxic respiratory failure; surfactant therapy established when indicated; and the presence of an arterial line. The exclusion criteria were congenital diaphragmatic hernia, major congenital anomalies including cyanotic, and significant congenital heart disease.

2.1. Outcomes

The primary outcome of the study was the OI ($PaO2 \times FiO_2$ $x100/PaO^2$) absolute values and change from baseline measured after the first dose, every 6 hours for 7 days or until infant extubated, and improvement in the OI was defined as a decrease of 10% from the previously calculated value. The secondary outcomes were hemodynamic parameters (absolute values and change from baseline measured after the first dose, after 24 hours, after 36 hours, after 48 hours, and every 12 hours thereafter for 7 days while receiving therapy); pulmonary arterial pressure in mm Hg measured by echocardiography; the practicality of administration; gastric tolerance; hypotension; renal function and liver function values; and all causes of mortality within the first 28 days of life.

2.2. Randomization and recruitment process

Once entry criteria had been met and family consent obtained, a previously prepared and closed-sealed envelope was opened by the designated pharmacist assigning the infants to either Group A [iNO combined with sildenafil therapy] or Group B [iNO combined with placebo]. None of the treating physicians, nurses, and/or respiratory therapists were aware of the nature of therapy. At the end of the study, the pharmacist disclosed the assignment of each group.

2.3. Ventilation management

Both conventional mechanical ventilation and high frequency ventilation were used according to the infant's clinical and radiological needs. Surfactant was offered when indicated clinically and or radiologically. The OI was calculated with every blood gas (mean airway pressure $\times$ FiO_2 $\times$ $1/PaO_2$).

Rebound episode was defined as increase FIO_2 requirement by more than 20% for a period of 12 hours that required increase of iNO.

2.4. Echocardiography

PPHN was confirmed by Doppler echocardiography demonstrating tricuspid regurgitation, size of the right ventricle, and systolic pulmonary artery pressure. A value of >40 mm Hg was considered to be high pulmonary hypertension. Doppler echocardiography was performed four times: at baseline before starting iNO, 48 hours after recruitment, at 7 days, and at 14 days [29, 30].

2.5. Biochemical investigations

Regular arterial blood samples to monitor gases in the blood were taken routinely every 4–6 hours until the discontinuation of iNO, and then every 8–12 hours until the discontinuation of mechanical ventilation.

2.6. Initiation and weaning from iNO gas

The starting dose of iNO was 20 ppm. Weaning from oxygen was carried out by 2–4% every hour

to keep $PaO_2 \leq 80$–90 mmHg and SO2 = 90–95%. Weaning from iNO started when FiO_2 requirements were reduced to less than or equal to 40% and when PaO2 was equal to or more than 80 mmHg. The weaning steps were as follows: five ppm every 6 hours if PaO_2 is more than 80 mmHg, once iNO reaches 5 ppm, weaning will be by 1 ppm every 2–4 hours. Weaning will be held if PaO_2 falls below 50 ppm. If PaO_2 falls to less than 50 mmHg, iNO will be increased to the previous level. During the process of iNO weaning, FiO_2 can be increased by 10% increments to compensate for the reduction of iNO dose provided that FiO_2 remains below 60%; otherwise, iNO will be increased to the previous level.

2.7. Sildenafil therapy

A 50 mg tablet was crushed into powder and diluted in 10 mL Orabase [suspension syrup agent] to prepare 5 mg/1 ml. All doses required for 48 hours were available, and solutions were stored at 2–8°C for one month. For the placebo, an equal volume of diluents was used [Orabase syrup] of the same color and viscosity. The infants in group (A) received 2 mg/kg of sildenafil every 6 hours, whereas the infants in group 9 (B) received normal saline as a placebo every 6 hours. Both drug and placebo treatment were given by orogastric tube [31].

2.8. The clinical approach for all infants followed these broad strategies [32]

No "hyperventilation" but avoidance of hypercarbia [i.e., $PacO_2$: 35–45 mmHg], endotracheal suction and manual ventilation only when needed (i.e. a severe episode of hypoxemia), avoidance of significant acidosis (i.e., maintain pH $\leq$ 7.3), no alkalosis (i.e., not aiming to keep pH >7.5), no routine $NaHCO_3$ infusion , Inotropes (dobutamine, dopamine, adrenalin) and volume infusion to try to preserve intravascular volume and maintain mean arterial BP at the 50th percentile, no Milrinone to be used , all infants are initially covered with antibiotics after initial blood culture and chest x-ray performed as needed. Complete blood count, serum electrolytes, and the renal and liver function profile were measured once at the beginning of the recruitment and every day in the first week of the study. Thereafter, they were measured once every week or as clinically needed.

3. Statistical methods

The sample size was calculated by the HMC research center. The overall international incidence is 1-2 cases per 1000 live births admitted to NICU compared with 1.6/1000 live births in our NICU. The calculated sample size was 75 newborns in each treatment group. We estimated the 80% power to detect a predefined difference (meaningful minimal detectable difference) of 20% in OI response between the two groups (increased response to 75% in the sildenafil group vs. 55% in the control group), with an alfa level of 0.05. The investigators were unable to grant funding for a multi-central participation in the study. After the three-years study period, we had recruited only 13 babies in the sildenafil group and 11 babies in the treatment group.

The data were normally distributed according to the Shapiro-Wilk test. Categorical variables such as gender and mode of delivery were analyzed using the Chi square test. Continuous variables such as the OI and laboratory values were analyzed by using the independent sample *t* test. The data were collected in MS Excel 2007 and the analysis was carried out using SPSS version 20.0. They were treated with the highest level of confidentiality. The study has been approved by the research committee at HMC. Parents of every patient were asked to sign HMC-approved consent forms before recruitment. The study continued for 28 days after recruitment, at death, if serious side effects attributed to the use of the drug, or if disqualified from the study.

4. Results

During the study period (September 2011 to September 2014), 51 newborn babies (term or late preterm> 34 weeks) were started on iNO within 48 hours of life, although only 24 of these were recruited into our study (Fig. 1). Twelve babies with PPHN were excluded from the analysis because they were syndromic or suffered from other complex congenital heart disease. Six babies had a congenital diaphragmatic hernia, two were diagnosed with hypoxic respiratory failure secondary to congenital protein B surfactant deficiency, three with HIE were recruited into another randomized interventional control trial, and the families of four newborns refused to consent. Of the 24 babies successfully recruited, 13 newborns received sildenafil in addition to iNO and 11 were in the placebo group (received only iNO). The

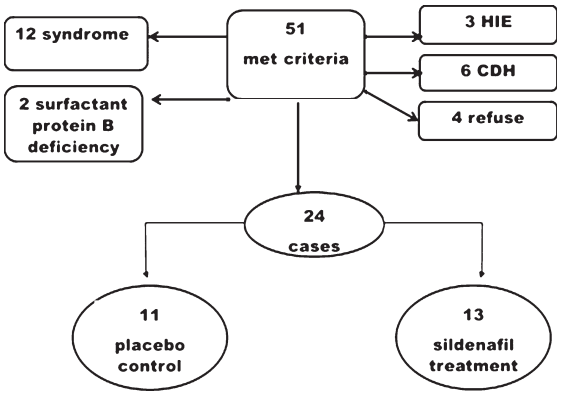

Fig. 1. Case recruitment process. During study period 51 babies newly born term or late preterm > 34 were started on INO within 48 hours.

diagnosis at time of recruitment was in both groups (Fig. 2).

There was no significant difference between the two groups in gestation age, birth weight, mode of delivery, and Apgar score. Most recruited babies were in-born (Table 1). At the starting point, the OI was slightly higher in the group (A) without statistical significance. There were no differences between the two groups regarding surfactant administration, pneumothoraces, and the underlying causes of PPHN. The most common causes of PPHN were meconium aspiration syndrome, pneumonia, and RDS (see Fig. 2).

Sildenafil or placebo treatment in the assigned patients started within 12 hours after starting iNO (mean 8 ± 7 hours versus 6 ± 6 hours). Overall, there was a significant improvement after initiating iNO in both groups. Rebound episodes were recorded as 6 episodes in group sildenafil group versus 5 episodes in placebo group. There was no meaningful statistical difference at any time point between the two groups; however, there was a tendency for better stabilization and fewer rebounds in the intervention group (Fig. 3). Both groups show no statistical differences regarding the WBC, platelet counts, coagulation profile, liver and kidney functions. No significant adverse effect noted in both groups (Tables 2 & 3).

5. Discussion

In this feasibility study, investigators were aiming initially to explore the potentials of adding oral sildenafil as an adjunctive therapy to iNO in order to augment the benefits of the pulmonary vasodilator effect of iNO. We were not aiming to assess the vasodilator effect of oral sildenafil. As well, we were assessing the tolerance of the oral medication by the newborn infants. The study monitored mean blood pressure, feeding intolerance, fluid balance, as well as renal and liver function. There was insignificant tendency to have lower blood pressure in the treatment group during the first 24 hours of starting sildenafil. The percentage of babies who needed inotropic support in both groups was similar (5/13 in the treatment group compared with 4/11 in the placebo group) (Fig. 4). However, the duration of treatment was higher in the treatment group.

Over the 14 day period of patient observation, all biochemical parameters indicated that the medication was safe, with no significant side effects recorded. Both renal and liver function parameters were normal in both groups. The only case of gastrointestinal

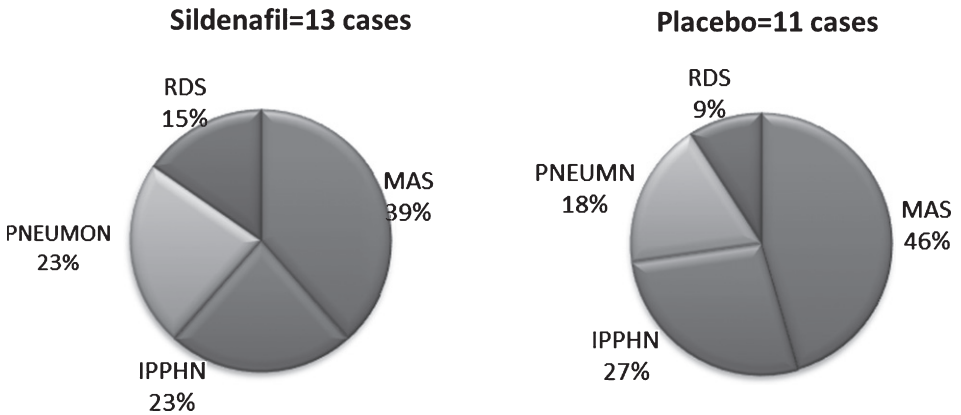

Fig. 2. Diagnoses of the study population.

Table 1
Demographic data of study of cases at time of recruitment

	Sildenafil 13	Placebo 11	*P*- valve
Male	7	8	0.3
Cesarean section as mode of delivery	12	9	0.4
Gestational age [weeks]	38.1[±2.3]	39 [±1.61]	0.3
Birth weight [grams]	3107 [±7]	3179 [±627]	0.7
Apgar at 1 minute	6.23 [±2.7]	6.64 [±2.29]	0.7
Apgar at 5 minutes	8.31 [±1.6]	8.73 [±1.19]	0.5
Apgar at 10 minutes	9.6 [±0.2]	9.5[±0.3]	0.2
Seizures	0/13	2/11	0.1
Intraventricular hemorrhage[a]	2[a]/13	0/11	0.1
Length of stay [days]	23.2 [±15.2]	17.81 [±11.5]	0.3
Age when iNO started [hours]	12.30 [±11.0]	19.54 [±16.6]	0.2
Hours when Sildenafil started [after iNO]	8.34 [±7.4]	6.50 [±5]	0.5
Total days of sildenafil use	11.46 [±4.9]	10.90 [±4.15]	0.8
Inotropic support	5	4	0.5
iNO total hours given	138.7[b] [±118.1]	98.72 [±83.5]	0.5
Mechanical ventilation days	10.23 [±8]	6.72 [±4.33]	0.2
Days on CMV	4.07 [± 3.6]	2.81 [±2.85]	0.3
Rebound episodes	6 episodes	5 episodes	0.15
Days on HFOV	6.15[b] [±7.5]	3.90 [±4.08]	0.4
Days on oxygen >21% FiO_2	11.46 [±9]	9.45 [±4.78]	0.5
Hours on oxygen 100% FiO_2	22 [±20.0]	28.36 [±27.5]	0.8
Number of surfactant doses given	1.30 [±1.0]	1.09 [±1.37]	0.6
Oxygen index at recruitment	29.9 [±10.1]	28.83 [±9.55]	0.3

[a]Intraventricular hemorrhage grade I and II.

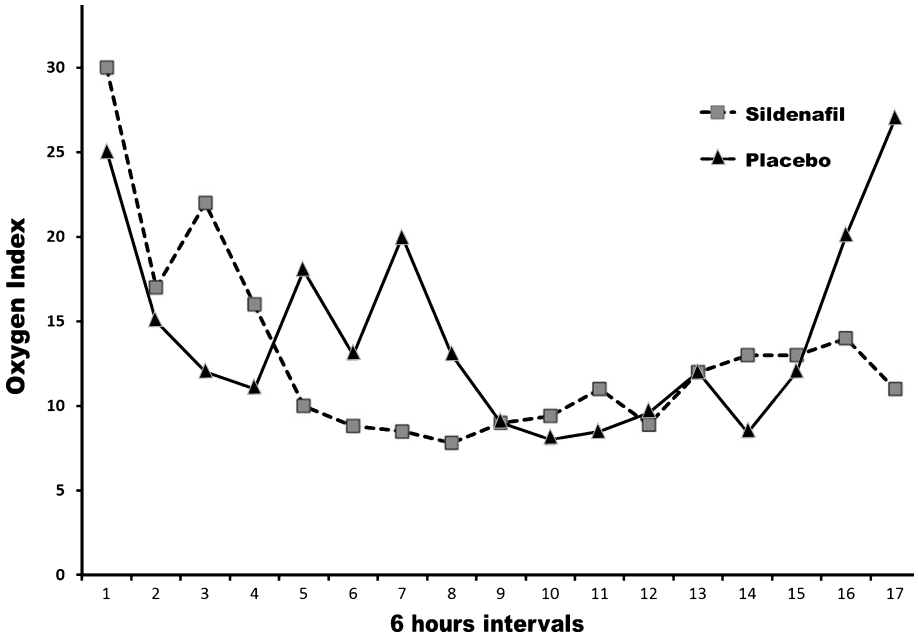

Fig. 3. Trend of mean oxygen index response in both study groups. The reduction in oxygen index seems more homogenous with less rebound events in the sildenafil group.

melena was recorded in the placebo group, while there were five cases of gastric bleeding (two in the treatment group and three in the placebo group).

Regarding respiratory support, in the sildenafil group, newborns needed iNO for an average of 138 hours compared with 98 hours in the control group; they also required a longer period of mechanical ventilation support (Table 1). The number of rebound attacks in the treatment group was less than that in the placebo group (Fig. 3).

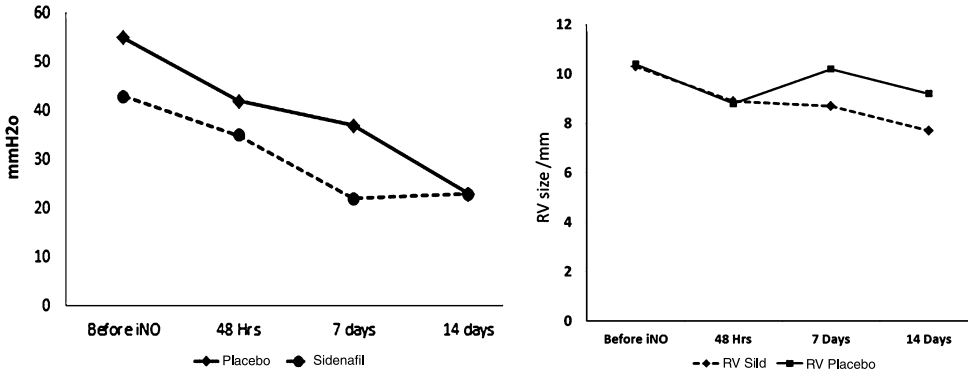

Fig. 4. Mean Pulmonary artery pressure and size of right ventricle measurement by Ecchocardiography. Normal value of right ventricular dimension for 39 weeks gestation & weight of 3–3.5 kg is 6–8 mm.

Table 2
Laboratory value: P-value ≤ 0.1

	Sildenafil	Placebo
Mean WBC count, $10^3/mm^3$	14.90 [±3.83]	14.52 [±6.40]
Mean neutrophil, %	56.58 [±13.57]	55.25 [±12.99]
Mean platelet count,$10^3/mm^3$	180.92 [±72.48]	196.91 [±83.34]
Mean prothrombin time, seconds	21.08 [±31.21]	11.72 [±1.38]
Mean APTT, seconds	50.29 [± 41.79]	42.32 [±7.61]
Mean serum urea, mmol/L	4.60 [±2.07]	3.60 [±1.49]
Mean serum creatinine, μmol/L	55.19 [±30.30]	47.87 [±28.07]
Mean serum AST, u/mm^3	68.81 [±70.59]	30.51 [±18.10]
Mean alkaline phosphatase, u/mm^3	192.65 [±62.12]	156.34 [±38.30]

APTT: activated partial thromboplastin time. AST: aspartate aminotransferase.

Table 3
Side effects: P-value ≤ 0.1

	Sildenafil	Placebo
ROP[a]	Nil	Nil
Late onset sepsis	3/13	2/11
Seizures	0/13	2/11
Vomiting	5/13	4/11
Hematemesis	2/13	3/11
Melina	0/13	1/11
Abdominal distension	3/13	4/11
Leukopenia	1/13	1/11
Low platelets count	7/13	5/11

[a]ROP: retinopathy of prematurity. All babies' received ROP screening before discharge.

The mean number of days of mechanical ventilation in the treatment group was 10 days (6 days on HFOV and 4 days on conventional ventilation), while this was shorter in the control group (7 days on average: 4 days on HFOV and 3 days on conventional ventilation). After extubation, newborns in the treatment group required noninvasive ventilation and oxygen supplementation for an average of 11 days compared with 9 days in the control group.

Sildenafil is available for oral administration; it is well absorbed by the gastrointestinal tract and starts acting 15 minutes after administration. It has a half-life of 4 hours, and it is excreted by the liver. The recommended dose for children ranges from 1 to 2 mg/kg/day [33, 34]. Herrera et al. [20] compared the conventional management of newborn infants with PPHN with and without the addition of sildenafil in the absence of iNO (sildenafil 13 cases, placebo 11 cases) and showed a significant improvement in the OI in the treatment group. In addition, PaO2 at 72 hours was better, while mean airway pressure and number of ventilation days were lower in the sildenafil group. A similar outcome was confirmed by other investigators [35, 36]. To the best of our literature search, two studies have discussed the idea of adding sildenafil to iNO. Both were conducted in completely different circumstances. One used intravenous sildenafil in older infants, while the second study used oral sildenafil in the adult population. Both studies were conducted in post-cardiac surgery and with post-ECMO patients. Despite pulmonary vasodilation, which enhanced the effect of iNO in both studies, sildenafil reduced systemic blood pressure, leading to systemic hypotension and, consequently, worsening oxygenation. In spite of the methodological limitations where the sample size was 15 and 20 patients, respectively, the study shows

concerns regarding the effect of sildenafil on systemic blood pressure [37, 38]. The available data from our current study indicated that adding oral sildenafil to iNO during the acute treatment of PPHN was safe with no significant adverse effects. As well, it resulted in smoother weaning of iNO. Further trials with larger sample size should confirm the benefits of adding sildenafil early.

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