Original Article

Intravenous Sildenafil for the Treatment of Persistent Pulmonary Hypertension of the Newborn in a Resource-Limited Setting

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Abstract

Introduction: Treatment of severe persistent pulmonary hypertension of the newborn (PPHN) is based on the administration of selective pulmonary vasodilators. Inhaled nitric oxide is the only vasodilator therapy approved by the Food and Drug Administration. Non-selective vasodilator such as sildenafil has been the treatment available administered orally in most developing countries to manage newborn with PPHN. The aim of the study was to describe the effects and tolerability of intravenous (IV) sildenafil, as a loading dose of 0.4 mg/kg, followed by a continuous infusion of 1.6 mg/kg for 72 h on the oxygenation index (OI) in neonates with PPHN. **Materials and Methods:** This was an exploratory observational prospective study. Newborns ≥35 weeks of gestational age, post-natal age ≤72 h, with PPHN and an OI ≥20 were included in the study. Sildenafil was administered intravenously as a loading dose of 0.4 mg/kg, followed by a continuous infusion of 1.6 mg/kg for 72 h. During the sildenafil infusion, monitoring of vital signs and respiratory parameters was performed. The data were analysed with the SPSS v21. **Results:** Twenty-five infants were included. A significant improvement (P = 0.01) of OI (at admission, median: 25 and interquartile range [IQR] = 8) was observed at the end of the loading dose (3 h) (18 IQR = 4) and at 72 h (7 IQR = 4). No serious adverse effects were observed. Before hospital discharge, seven patients died. **Conclusions:** IV sildenafil administered, in newborns with PPHN with an IO ≥20, improved oxygenation in most of the patients without serious side effects.

Keywords: *Oxygenation index, persistent pulmonary hypertension of the newborn, sildenafil*

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Introduction

Chemical mediators play a central role in regulating foetal lung pressure and the normal transition to extrauterine life.[1] Persistent pulmonary hypertension of the newborn (PPHN) results from a failure of the normal circulatory transition at birth. It is characterised by sustained elevation of pulmonary vascular resistance, with normal or low peripheral vascular resistance.[2] The incidence ranges from 0.4 to 6.8/1000 live births. The mortality rate varies from 4% to 33%, which is higher in developing countries.[3]

Treatment of severe PPHN is based on the administration of selective pulmonary vasodilators. Inhaled nitric oxide (iNO) is the only vasodilator therapy approved by the Food and Drug Administration for the treatment of PPHN.[4] Nitric oxide mediates pulmonary vasodilation through soluble guanylate cyclase and cyclic guanosine monophosphate (cGMP).[5,6] However, between 30% and 40% of patients with PPHN do not respond to iNO. Furthermore, the studies showed no reduction on the

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need for extracorporeal membrane oxygenation (ECMO) or adverse effects on neurodevelopment.[7,8]

The iNO is a costly treatment, not available in most developing countries. In many of these countries, sildenafil is prescribed as an off-label treatment of PPHN.[9] It is administered, from the crushed tablet (50 mg), diluted and by nasogastric tube.[10]

Sildenafil (citrate) inhibits phosphodiesterase type 5, an enzyme predominant in the lung tissue, that is a key regulator of newborn vascular reactivity. Its activity inhibition increases cGMP concentration and results in pulmonary vasodilation.[1] A Cochrane systematic review found that sildenafil improved oxygenation and reduced mortality in PPHN neonates.[11] Intravenous (IV) administration began to be used in patients undergoing cardiac surgeries with good tolerance, optimal response, very few side effects and stability of IV preparation.[12-14] Steinhorn *et al*. in a dosing escalating study of IV sildenafil in 36 neonates with PPHN found a significant improvement in oxygenation index (OI) without severe adverse. According to the results, the authors suggested a loading dose of 0.4 mg/kg delivered over 3 h, followed by a maintenance infusion at 1.6 mg/kg/day for 72 h[15] for future clinical studies. The safety of this dosing has been verified in newborns with congenital diaphragmatic hernia (CDH).[16,17]

In most hospitals of the county where the study was carried out, the mainstay treatment of PPHN is sildenafil administered by nasogastric tube from crushed tablets, due to the limited iNO availability. In this context, the goal of the present study was to describe the effects on the OI and the tolerability of IV sildenafil administered at a dose of 0.4 mg/kg, as a loading dose in 3 h, followed by a continuous infusion of 1.6 mg/kg/day, for 72 h, in neonates with PPHN, with an OI ≥20 as an alternative to oral administration from crushed tables, a resource-limited setting.

Materials and Methods

An observational prospective study was performed between October 2019 and January 2021 at the neonatal intensive care unit (NICU) of the Social Security Hospital in Asuncion, Paraguay. This hospital is equipped with high-frequency oscillatory ventilation (HFOV), partial availability of iNO and no ECMO available.

Eligible infants for the study were newborns with gestational age ≥35 weeks and post-natal age ≤72 h, with suspected pulmonary hypertension, confirmed by echocardiography. A certified paediatric cardiologist performed Doppler echocardiography and the diagnosis of PPHN was made if a bidirectional or continuous right-to-left shunt across the foramen oval or ductus arteriosus with no congenital heart diseases was present.

Neonates were included in the study if they had an OI ≥20 and the informed consent of the parents. Exclusion criteria included congenital malformations, hypotension (mean arterial pressure [MAP] <35 mmHg), seizures and signs of shock, anaemia (haemoglobin <9 g/dl), thrombocytopenia (platelets <50,000/mm^3), leucopenia (white blood cells <2500/mm^3), serum creatinine with double upper limit value, alanine aminotransferase and aspartate aminotransferase 3 times above the normal values for age and direct bilirubin >2 mg/dl.

Demographic and perinatal data of the mothers and newborns were recorded. Other variables studied were post-natal age at study admission, pathologies accompanying the PPHN, respiratory parameters, pulmonary pressure and hospital stay. Adverse events such as hypotension, patent ductus arteriosus, seizures, the sign of shock, bleeding disorders and metabolic acidosis were monitored.

The main outcome was the changes in OI in the sildenafil infusion. The secondary outcome was the presence of adverse effects.

Sildenafil infusion and monitoring

The neonates who met the inclusion criteria received sildenafil (12.5 ml solution for injection containing 10 mg of sildenafil citrate, Atlantic Pharma, India) approved by the National Health Surveillance Office of Paraguay, study number 001/19 (DINAVISA, by its acronym in Spanish), as exclusive use for the present study.

Sildenafil was diluted in 5% dextrose solution with a loading dose of 0.4 mg/kg in continuous infusion for 3 h, followed by a continuous infusion of 1.6 mg/kg/day for 72 h.

Monitoring during the sildenafil infusion included heart and respiratory rates, systolic and diastolic blood pressure, OI, partial pressure of oxygen (PaO_2) and inspired fraction of oxygen (FiO_2) every 30 min for the first 3 h and every 12 h thereafter until the end of the infusion (72 h). Echocardiography at 24, 48 and 72 h during sildenafil infusion was performed.

PPHN clinical management protocol of the Neonatal Handbook of the Ministry of Health of the country[18] was used at the NICU by the attending neonatologist of the hospital. It recommends keep the MAP between 50 and 60 mmHg, pre-ductal oxygen saturation between 91% and 96% and pH >7.35. Inotropic as needed, dobutamine 10–20 μg/kg/min or adrenaline 0.01–1 μg/kg/min, with

OI >20 start iNO and HFOV according to hospital availability. When iNO is not available, recommend start sildenafil orally (by nasogastric tube) at a dose of 1–2 mg/kg every 6 h for 72 h.

In the presence of serious adverse effects, or at any time that the staff deemed necessary, the medication should be discontinued. Data on the evolution of the patients, until hospital discharge and thereafter up to 12 months of age were collected.

The data were analysed with the SPSS v221 program (IBM, NY, USA). Qualitative variables were expressed in percentages and quantitative variables in means with standard deviation or median with quartile according to their distribution. The comparison of the IO values at admission, at 3, 24, 48 and 72 h was performed by the sum of Wilcoxon ranges. The comparison of the Score for Neonatal Acute Physiology-Version II (SNAP II) score between the deceased and the survived newborns was carried out using the Student's *t*-test. $P = 0.05$ was considered significant.

The study protocol was approved by the institutional review board (IRB N° 00006311-Office for Human Research Protection) with the informed consent of the parents or guardians, in accordance with the tenets of the Helsinki Declaration.

Results

A total of 25 infants were included, 64% (16/25) of them were delivered by caesarean section and half (8/16) had no previous labour. The mean gestational age of the neonates was 36.8 ± 1.2 weeks and the post-natal age at study entry was 31.5 ± 17.3 h. Other perinatal data are shown in Table 1.

At admission, the median OI was 25, interquartile range (IQR) = 7.5 and at the end of the loading dose (3 h) 18 IQR = 3.5; $P = 0.001$. At 24 h, it was 15 IQR = 3.5; $P = 0.001$ and at 72, it was 7 IQR = 4; $P = 001$; Wilcoxon test, respectively. Pulmonary pressure as measured by Doppler echocardiography, performed in 17 neonates at 24, 48 and 72 h, also decreased. The PaO_2, FiO_2 and median systolic and diastolic blood pressure during sildenafil infusion are presented in Table 2.

Figure 1 shows the OI trend at admission and during the sildenafil infusion.

All patients received antibiotics and inotropic (dopamine and adrenaline) and sedation with morphine or fentanyl. During the loading dose, two patients presented moderate hypotension attributable to sildenafil, which responded to the increased dose of inotropic. No patients had other complications attributable to sildenafil. Five

Table 1: Perinatal characteristics of the mothers and newborns (*n*=25)

Variables	Values
Maternal characteristics	
Maternal age, mean±SD[a]	25.6±5.4
Delivery, *n* (%)	
Vaginal	9 (36)
Caesarean section	16 (64)
Neonatal characteristics	
Sex, *n* (%)	
Female	11 (44)
Male	14 (56)
Birth weight (g)	3313.8±387
Gestational age (weeks)	36.8±1.2
Post natal age in hours[a]	31.5±17.3
Apgar 1 min	4.7±1.6
Apgar 5 min	6.8±1.4
SNAP II score	44.9±11.7
Primary diagnosis, *n* (%)	
Respiratory distress syndrome	7 (28)
Meconium aspiration syndrome	6 (24)
Early sepsis	5 (20)
Perinatal asphyxia	4 (16)
Idiopathic PPHN	1 (4)
Diabetic mother	1 (4)
Metabolopathy	1 (4)

[a]It indicate the meaning of the acronym. The mother´s age is expressed as a mean with standard deviation. SD - Standard deviation; SNAP II - Score for Neonatal Acute Physiology-Version II; PPHN - Persistent pulmonary hypertension of the newborn

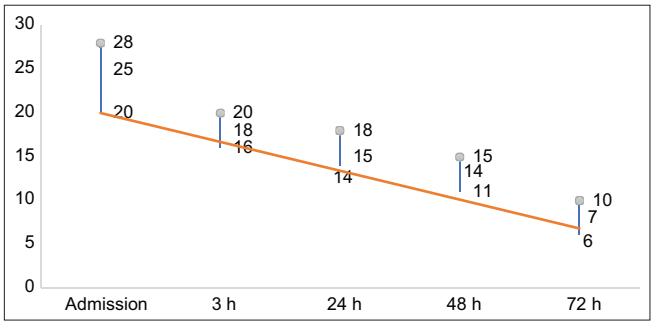

Figure 1: Trend of OI values during IV sildenafil infusion in neonates with PPHN, expressed as median and Q1–Q3 values ($n = 25$). IV: Intravenous, OI: Oxygenation index, PPHN: Persistent pulmonary hypertension of the newborn

out of 25 newborns received surfactant 2 doses and 9/25 blood transfusion. iNO was administered in three patients before sildenafil infusion. The HFOV was used in 10/25 newborns.

Sildenafil infusion was discontinued in two patients, including a newborn with persistent metabolic acidosis, due to probable organic acidosis, who died within 24 h of life. One patient with birth asphyxia and severe persistent hypertension of the newborn (PPRN), receiving iNO and HOFV, died within 24 h of life.

Table 2: Respiratory parameters, blood pressure and echocardiography at admission and during the sildenafil infusion (*n*=25)

Median (Q1–Q3)	Admission	3 h	24 h	48 h	72 h
IO (%)	25 (20–28	18 (16–20)	15 (14–18)	14 (11–15)	7 (6–10)
PaO_2 (mmHg)	45 (42–48)	62 (60–72)	78 (66–80)	84 (70–90)	90 (75–92)
FiO_2 (%)	100 (100–100)	80 (80–85)	65 (61–70)	59 (55–60)	40 (35–40)
SBP (mmHg)	50 (48–52.5)	65 (57–71)	70 (60–73)	70 (68–71)	70 (70–76)
DBP (mmHg)	28 (25–34)	34 (28–36)	35 (30–37)	35.5 (33.7–38)	35 (30–37)
Doppler (mmHg)	35 (28–50)		20 (18–25)	18 (17–19.5)	18 (15–17)
Ecocardiography					

PaO_2 - Partial pressure of oxygen; FiO_2 - Inspired fraction of oxygen; SBP - Systolic blood pressure; DBP - Diastolic blood pressure; OI - Oxygenation index

Before hospital discharge, five patients died with a mean of 8.8 ± 1.7 days of length of stay. Therefore, the in-hospital mortality was 7/25 (28%). The mean SNAP II score was 56.8 ± 6.7 in infants who died versus 40.2 ± 9.7 in survivors (P = 0.001, Student's t-test). Eighteen patients survived, with a mean of 9.8 ± 4 days of the length of stay. After hospital discharge, three patients died before 6 months of age.

Discussion

This study was carried out in a limited-resource facility where iNO and HFOV are not always available. The dose of the IV continuous sildenafil infusion, used in this study, decreased OI without serious adverse events. Although all the newborns met the criteria to receive iNO, its unavailability led to the use of sildenafil as the sole pulmonary vasodilator therapy in most patients; only three patients received iNO therapy.

We found an early improvement in oxygenation after the loading dose of sildenafil, which was sustained during the infusion of the maintenance doses, with two cases of mild hypotension that resolved with increased inotropic doses. However, there were 2 sildenafil and no responders. One of them, on combined HFOV/sildenafil/iNO therapy died within 24 h of life, with a diagnosis of severe PPHN, perinatal asphyxia and seizures, and the other one on combined sildenafil/HFOV therapy, died shortly after 24 h of age, due probable diagnosis of organic acidemia. Non-responders in our study were lower than the 58% reported by Kipfmueller *et al*., who administered the same dose of IV sildenafil, than we used, in 26 neonates with CDH and an OI of 15.[17]

Unlike our population, in the study of Steinhorn *et al*., most neonates, at the time of starting sildenafil, were treated with iNO. Seven patients who did not meet the criteria for iNO treatment received sildenafil as a sole pulmonary vasodilator, and only one patient went on to receive iNO. More than half of this group (5/7) received the higher infusion doses, like that used in our study.[15] According to the authors, this IV dose would be the equivalent of approximately 4 mg/kg/day of the oral dose, administered in clinical studies of oral sildenafil.[11,19] Cochius et found appropriate sildenafil plasma levels, with the same dose scheme of our study, in 23 neonates with CDH.[16]

Pierce *et al*. found that IV sildenafil at a loading dose of 0.1 mg/kg administered within 30 min, followed by a maintenance dose of 0.03 mg/kg/h, versus placebo in neonates with PPHN receiving iNO treatment, did not decrease the rate of treatment failure, 27.6% versus 20% in the sildenafil and placebo group, respectively. The study found hypotension and hypokalaemia as adverse effects.[20]

Although IV sildenafil improved oxygenation in 23/25 patients, the in-hospital mortality rate was high. The newborns who did not survive had a higher severity score (SNAP II) than survivors. Nakwan *et al*. found that newborns with PPRN and a SNAP II score ≥43 had the greatest mortality risk.[21] The severely ill neonates underwent invasive procedures which expose them to infections linked to venous and arterial access routes.[22]

The PPHN mortality rate is higher in developing countries compared to more developed countries, due to limited diagnosis and treatment resources.[9] The overall mortality in newborns with PPRN was 7.3% in a study conducted in the USA.[23] While in a Malaysian study carried out in a hospital with iNO availability, PPHN mortality was 16.4%.[24]

After hospital discharge, three patients with neurological sequela died before 6 months of age. A population-based study in California USA showed that patients with PPHN have 3.5 times (95% confidence interval = 3.3–3.7) more risk of dying in the 1st year of life as compared to patients without PPHN.[25]

PPHN is a serious pathology, and the sequelae depend on the underlying disease. Reported neurodevelopmental

disorders range from 14% to 46%, among which are neural sensory deafness, cerebral palsy and cognitive and motor impairments.[23] Although the risk of ocular complications in neonates treated with sildenafil remains unclear, two studies did not find ophthalmic complications in term and near-term neonates with PPHN, who received oral sildenafil.[26,27]

In this study, sildenafil was the only pulmonary vasodilator used together with the general measures in most neonates with severe PPRN that warranted treatment with iNO. The high in-hospital mortality rate may be related to this condition. However, the study provides data on the effects on the OI and the tolerability of IV sildenafil, at the doses administered, in newborns with PPHN. It was also possible to corroborate the absence of serious adverse effects, in concordance with other studies.[15,20] The use of IV sildenafil is an alternative to oral administration from crushed tablets either as adjuvant treatment or as compassionate treatment of PPHN in countries with the unavailability of iNO.

The gold standard of HPPRN treatment remains iNO and the means for availability should be sought in public hospitals mainly, where the most of birth in the country take place. However, other therapeutic alternatives are still being sought considering that iNO has a 30%–40% non-response,[28] including nebulized magnesium sulphate.[29] In developed countries, when this occurs, the next one in the treatment escalation is restricted to the ECMO.

Limitations

This study has some limitations, mainly the sample size. Delay in obtaining IV sildenafil approval by the National Health Surveillance Office of Paraguay and the SARS-CoV-2 pandemic prevented a multicenter study with a higher number of participants. Further, sildenafil blood concentration was not measured. On the other hand, the evidence on the efficacy of sildenafil in PPHN and the lack of availability of other new therapeutic alternatives prevented carrying out a controlled clinical study. The results must be corroborated with a greater number of patients and evaluate the administration of IV sildenafil in neonates with PPHN and an OI ≥15 in resources limited setting.

Conclusions

In this exploratory observational study in a limited resources facility, the IV sildenafil at the loading dose of 0.4 mg/kg for 3 h following continuous infusion at 1.6 mg/kg/day, for 72 h in the newborns with PPHN, with an IO ≥20, improved oxygenation in 92% of the patients without serious adverse effects. Although the mortality before hospital discharge was high.

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Conflicts of interest

There are no conflicts of interest.

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