Original Article

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Paediatrics Section

Effect of Sildenafil in Neonates with Persistent Pulmonary Hypertension: An Interventional Study

JIGAR JAIN[1], JOLLY VAISHNAV[2], ARIF VOHRA[3], MANSI SHAH[4], ANIKA GOYAL[5]

ABSTRACT

Introduction: Persistent Pulmonary Hypertension of the Newborn (PPHN) reflects a disruption of the normal perinatal circulatory transition and is characterised by high pulmonary artery pressure. Inhaled Nitric Oxide (iNO) is considered the mainstay of treatment for PPHN. However, many developing and resource limited countries do not have access to such expensive therapy. Therefore, sildenafil, due to its easy availability and low cost, becomes the most commonly used drug in the management of PPHN in such settings.

Aim: To study the treatment response and outcomes of neonates who received sildenafil for the management of PPHN.

Materials and Methods: The present hospital-based prospective interventional study was conducted in the Neonatal Intensive Care Unit (NICU), BJ Medical College, Civil Hospital, Ahmedabad, Gujarat, between May 1, 2020, and April 30, 2021. Study was conducted on neonates with meconium aspiration syndrome and/or severe birth asphyxia admitted to the NICU. A total of 48 neonates with Two Dimensional (2D) echocardiography-proven PPHN were enrolled. Baseline clinical parameters including heart rate, respiratory rate, preductal and postductal Saturation of Peripheral Oxygen (SpO_2), Oxygenation Index (OI), Saturation Oxygen Distending Pressure Index (SOPI), and Non Invasive Blood Pressure (NIBP) were monitored every six hours. Neonates who were on invasive/non invasive ventilation had their Fraction of Inspired Oxygen (FiO_2), Positive End Expiratory Pressure (PEEP), Peak Inspiratory Pressure (PIP), respiratory rate and flow rate monitored every six hours. Data were statistically analysed using Analysis of Variance (ANOVA) test.

Results: During the study period, a total of 1080 neonates were admitted with meconium aspiration syndrome and/or severe birth asphyxia, out of which 48 neonates showed findings suggestive of PPHN on 2D echocardiography. A statistically significant improvement in oxygenation after sildenafil treatment was indicated by a significant reduction in OI from 35.3±8.6 to 13.2±2.1 (p-value <0.001), a reduction in SOPI from 3.6±0.3 to 1.5±0.2 (p-value <0.001), a reduction in FiO_2 (%) from 94.6±8.19 to 24.2±4.5 (p-value <0.001), an increase in Partial pressure of oxygen (PaO_2) (mmHg) from 52±5.6 to 72±3.4 (p-value <0.001), and an increase in SpO_2 (%) from 83.5±8.6 to 93.5±5.1 (p-value <0.001).

Conclusion: The findings of the present study suggest that oral sildenafil can be successfully used to improve oxygenation in patients with PPHN, especially in a resource limited setting where facilities like Extracorporeal Membrane Oxygenation (ECMO) and iNO are not available, as demonstrated in the present study.

Keywords: Clinical parameters, Echocardiography, Oxygenation index, Pulmonary artery

INTRODUCTION

The PPHN reflects a disruption of the normal perinatal foetal to neonatal circulatory transition [1]. The disorder is characterised by sustained elevation in Pulmonary Vascular Resistance (PVR) rather than the decrease in PVR that normally occurs at birth [2]. PPHN affects 2-6/1,000 of live births or approximately 10% of all infants admitted to neonatal intensive care and is accompanied by an 8-10% risk of death and significant short-term and long-term morbidity [3]. In neonates with PPHN, the pulmonary vasodilator iNO is considered the mainstay of treatment, and in resistant cases, ECMO is used [4]. However, many developing countries and resource limited centers do not have the funds or the technical expertise required for these expensive therapies [4]. Sildenafil, a phosphodiesterase-5 inhibitor that increases endogenous Nitric Oxide (NO) by inhibiting its metabolism, offers promise for the treatment of PPHN. Small randomised controlled trials performed in circumstances in which iNO and high frequency ventilation were not available, have demonstrated the utility of sildenafil oral therapy (1-2 mg/kg/dose every six hours) [1,2]. Because of its easy availability, it is the most commonly used drug in the management of PPHN and also known as the "poor man's NO". Though it is widely used across the nation, limited data about the efficacy of the drug in PPHN is available. Hence, the present study was aimed to study the treatment response and outcome of neonates who received sildenafil for the management of PPHN.

MATERIALS AND METHODS

The present hospital-based prospective interventional study was conducted in the NICU, BJ Medical College (tertiary care centre), Civil Hospital, Ahmedabad, Gujarat, India, over a period of one year from May 1, 2020 to April 30, 2021. The study was conducted after obtaining Institutional Ethical Committee Clearance (IEC reference number-47/2021).

Inclusion criteria: Neonates with a gestational age of more than or equal to 28 weeks who were admitted for severe birth asphyxia and/or meconium aspiration syndrome and were diagnosed with PPHN with 2D echocardiography were included in the study.

Exclusion criteria: Neonates with a gestational age less than 28 weeks and neonates who had only clinical signs of PPHN but normal 2D echocardiography were excluded from the study.

Sample size: Within the study duration, neonates who presented with PPHN following the inclusion criteria were enrolled in the study by convenient sampling.

Study Procedure

Neonates with meconium aspiration syndrome and/or severe birth asphyxia with clinical signs of PPHN on examination (hypoxaemia refractory to oxygen therapy, difference in preductal and postductal oxygen saturation >10%, differential cyanosis, and loud P2) [1] were subjected to 2D Echo for the diagnosis of PPHN by a paediatric cardiologist, as early as, possible. Neonates who had the following 2D echo findings suggestive of PPHN-Tricuspid regurgitation and/or right ventricular hypertrophy and/or right to left shunt in the foramen ovale/ductus arteriosus and/or interatrial or interventricular septum bowing to the left or appearing flattened were studied in detail [1]. Basic details of these enrolled neonates were recorded in a prestructured proforma. Their baseline reports-Complete Blood Count (CBC), C-reactive Protein (CRP), blood culture, Arterial Blood Gas Analysis (ABGA) chest X-ray, and other relevant investigations based on the clinical condition were done, as and when required for diagnostic purposes and recorded in the proforma. These neonates were started on sildenafil therapy. Oral sildenafil was given via a nasogastric tube with a starting dose of 1 mg/kg/dose and increased by 0.5 mg/kg/dose to a maximum of 2 mg/kg/dose every 6-12 hourly after assessing every six hours, if non responsive [1]. At the initiation of the drug, baseline clinical parameters, preductal and postductal SpO_2, OI, SOPI, NIBP were recorded in the proforma and were monitored every six hours until these neonates were weaned from oxygen support. Neonates were monitored for flushing/rash, diarrhoea, vomiting and hypotension. Follow-up 2D echocardiography was done at 14 days of life to assess the response outcome. Babies were considered responsive to therapy if at least two out of the three indicators present from the baseline values: Oxygen Saturation of Arterial blood (SaO2) >10% increase in ABG analysis, OI decreases by 10% (change from baseline measured after the 1st dose, every six hours for seven days or until the infant was extubated) and a decrease in FiO_2 by 5-10%. Neonates were considered unresponsive to sildenafil if there was no significant fall in OI after eight doses [3]. Sildenafil therapy was discontinued when OI <15 or hypotension despite the baby being on inotropes or no significant fall in OI after eight doses (non responsive) [3]. All these parameters were recorded in the presentation, proforma and results were evaluated.

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for Social Sciences (SPSS) software version 14.0. All data are presented as mean±Standard Deviation (SD) and values of p-value <0.05 were considered statistically significant. To compare categorical variables between groups, ANOVA test was used.

RESULTS

During the study period, a total of 1080 neonates were admitted with meconium aspiration syndrome and/or severe birth asphyxia, of which 200 neonates had clinical signs suggestive of PPHN. Out of these 200 neonates, only 48 neonates (28 males and 20 females) had findings suggestive of PPHN in 2D echocardiography and they were studied in detail. In the study group, 20 neonates had severe birth asphyxia, 16 neonates had meconium aspiration syndrome, and 12 neonates had both severe birth asphyxia and meconium aspiration syndrome. The mean age of echocardiography diagnosis was 31.2±6.9 hours. The mean duration of sildenafil therapy in the present study was 6.8±3.2 days. The mean cumulative duration of oxygen therapy in the present study was 10±2.9 days [Table/Fig-1]. A statistically significant improvement in oxygenation after sildenafil treatment was indicated by a significant reduction in OI from 35.3±8.6 to 13.2±2.1 (p-value <0.001), a reduction in SOPI from 3.6±0.3 to 1.5±0.2 (p-value <0.001), a reduction in FiO_2 (%) from 94.6±8.19 to 24.2±4.5 (p-value <0.001), an increase in PaO_2 (mmHg) from 52±5.6 to 72±3.4 (p-value <0.001), and an increase in SpO_2 (%) from 83.5±8.6 to 93.5±5.1 (p-value <0.001) observed over a period of 14 days [Table/Fig-2]. The mean time required to reach SpO_2 of >89% with oxygen supplementation (including invasive and non invasive ventilation) was 2.0±0.3 days after the initiation of sildenafil. The mean time required between starting sildenafil and the FiO_2 requirement reaching less than 40% was 12.4±2.2 days. The mean duration between starting sildenafil and the normalisation of OI was 13.4±3.2 days [Table/Fig-3]. No significant difference in mean BP between presildenafil and postsildenafil measurements was noted (p-value=0.54) [Table/Fig-4]. Hypotension was observed

Parameters		No. of neonates with PPHN (n=48)
Male to female ratio		1.4:1 (n=48) (28 males, 20 females)
Nutritional status, n (%)	AGA	32 (67%)
	SGA	16 (33%)
Co-morbid condition, n (%)	Severe birth asphyxia	20 (42%)
	Meconium aspiration syndrome	16 (33%)
	Meconium aspiration syndrome with severe birth asphyxia	12 (25%)
Mean±SD age of enrollment and starting sildenafil in study population		15.6±4.3 hours
Mean±SD age of echocardiography diagnosis (hours)		31.2±6.9 hours
Mean±SD dose of sildenafil in study population		6.8±0.7 mg/kg/day
Mean±SD duration of sildenafil therapy		6.8±3.2 days
Cumulative duration of oxygen therapy (days) (Mean±SD)		10±2.9 days
Mean±SD duration of mechanical ventilation		6.6±3.2 days
Mean±SD duration of hospital stay		11.3±2.7 days

[Table/Fig-1]: Baseline parameters.
AGA: Appropriate for gestational age; SGA: Small for gestational age

Parameters	0 hour* (n=48)	6 hour (n=46)	12 hour (n=45)	24 hour (n=44)	48 hour (n=40)	72 hour (n=36)	7 days (n=32)	14 days (n=30)	p-value (ANOVA test)
PaO_2 (%)	52±5.6	56±5.8	58±6.1	59±6.4	61±5.8	63±5.2	66±4.8	72±3.4	**<0.001**
SpO_2 (mmHg)	83.5±8.6	84.6±7.6	86.8±8.8	89.6±8.7	92.2±7.4	93±7.1	92.6±6.4	93.5±5.1	**<0.001**
OI	35.3±8.6	34.2±8.9	33.4±9.1	32.5±7.5	31.4±6.8	26.8±6.6	22.4±6.1	13.2±2.1	**<0.001**
SOPI	3.6±0.3	3.4±0.7	3.3±0.8	3.1±0.4	2.8±0.3	2.5±0.4	2±0.3	1.5±0.2	**<0.001**
FiO_2 (%)	94.6±5.19	90.3±7.15	88.6±8.8	85.2±7.5	83.6±6.4	80±6.2	58.5±5.2	24.2±4.5	**<0.001**

[Table/Fig-2]: Blood gas and clinical parameter changes following treatment with sildenafil.
After enrollment in the study; *0 hour is the time when sildenafil therapy was started; OI: Oxygenation index; SOPI: Saturation oxygen distending pressure index; The p-value in bold font indicates statistically significant value

Observed parameter	Mean±SD duration
Time require to reach SaO_2 of more than 89 with oxygen supplement (days)	2.0±0.3 days
Time interval to normalisation of ABG (days)	2.45±0.6 days
Duration between starting of sildenafil and FiO_2 requirement of less than 40%	12.4±2.2 days
Duration between starting of sildenafil and normalisation of SOPI	13.2±3.3 days
Duration between initiation of sildenafil and stopping of oxygen therapy (including invasive and non invasive ventilation)	14.2±3.2 days
Duration between starting of sildenafil and normalisation of OI	13.4±3.2 days

[Table/Fig-3]: Sildenafil response in survivors with PPHN.

Time after starting sildenafil	Mean arterial pressure recorded two hour after every dose of sildenafil	p-value (ANOVA test)
0 hour	42±5.6	p-value=0.54
2 hour	41±4.8	
8 hour	50±6.4	
14 hour	43±3.2	
20 hour	43±4.8	
26 hour	52±3.6	
50 hour	44±6.8	
74 hour	42±7.1	
7 days	45±4.5	
14 days	44±6.5	

[Table/Fig-4]: Comparison of mean arterial pressure before and after sildenafil therapy.

in only three neonates (6.25%) treated with sildenafil, and although it was not significant enough to cause discontinuation of the drug. Fourteen (70%) neonates who had severe birth asphyxia, 12 (75%) neonates with meconium aspiration syndrome, and 4 (33%) neonates with both meconium aspiration syndrome and severe birth asphyxia survived. The survival rate is significantly lower in neonates with both meconium aspiration and severe birth asphyxia (p-value=0.05).

DISCUSSION

The PPHN is characterised by a failure of the normal neonatal circulatory transition, resulting in marked pulmonary hypertension. Patients are often critically ill and require immediate ventilation. The reported incidence of PPHN is 0.43-6.8 per thousand newborns worldwide [4]. In the present study, authors prospectively reviewed the outcomes of neonates with PPHN who were treated with sildenafil. Although NO is the treatment of choice for PPHN, in many other low-resource countries like India where this therapy is unavailable, sildenafil is a promising alternative. Sildenafil, a specific Phosphodiesterase 5 (PDE-5) inhibitor, is a vasodilator specific to the pulmonary vasculature. The results of the present study indicate the effectiveness of sildenafil in improving oxygenation in neonates diagnosed with PPHN. During the study period, a total of 200 neonates with clinical signs of PPHN were identified and recruited for the study, out of which 48 neonates had findings suggestive of PPHN on 2D echocardiography. The mean age of enrollment in the present study was 15.6±4.3 hours, which are comparable to the study by Sayed A and Bisheer N reported 14.6±6.3 hours [5].

The mean age of echocardiography diagnosis in the present study was 31.2±6.9 hours, whereas Al-lawama M et al., reported a mean age of echocardiography diagnosis of 72 hours [6]. This early diagnosis could be due to the availability of a paediatric cardiologist at our affiliated cardiac institute. It is recommended to perform echocardiography on newborns with meconium aspiration syndrome and severe birth asphyxia within 24 hours of birth. Out of 200 neonates clinically diagnosed, only 48 (24%) had echocardiographic findings suggestive of PPHN, hence it is recommended to conduct echocardiography for the diagnosis of PPHN.

In the present study, at the time of admission, the mean FiO_2 (%) requirement was 94.6±5.1, mean PaO_2 (mmHg) was 52±5.6 with maximum oxygen support, and the mean OI was 35.3±8.6. In comparison, Steinhorn RH et al., reported a mean FiO_2 (%) of 88±1.6, a mean OI of 27.7±4.2, and a mean PaO_2 (mmHg) of 65.8±24.7 with maximum oxygen support, indicating the severity of the disease [7]. Most of the newborns were mechanically ventilated at admission, and their respiratory rate was set according to the ventilator. Therefore, it was not feasible to monitor the actual respiratory rate throughout the entire course of treatment.

The mean age of starting sildenafil therapy in the present study was 15.6±4.3 hours, which is lower than the findings of Sayed A and Bisheer N (26.8 hours), Baquero H et al., (24 hours), and Gupta A et al., (35 hours) [5,8,9]. This may be because the authors initiated sildenafil based on clinical criteria, and later these neonates underwent 2D echocardiography for confirmation of PPHN. Neonates who did not exhibit any signs of PPHN on 2D echocardiography were excluded from the study.

The mean duration of sildenafil therapy in the present study was 6.8±3.2 days. The mean dose of sildenafil therapy in the present study was 6.8±0.7 mg/kg/day, which was comparable to the study by Baquero H et al., where the mean dose of sildenafil therapy was 7 mg/kg/day in patients with moderate to severe PPHN [8]. Thereby the authors here, recommends initiating sildenafil therapy in neonates with moderate to severe PPHN at a dose of 6-8 mg/kg/day to achieve favourable outcomes. If the neonate does not show improvement with the maximum dose of sildenafil, it is advisable to consider switching to another pulmonary vasodilator or addressing any other associated co-morbid condition.

In the present study, the mean duration of sildenafil therapy was 6.8±3.2 days. In comparison, Sayed A and Bisheer N, Hussain AS et al., and Gupta A et al., reported mean durations of sildenafil therapy of 2.7±1.6 days, 12.6 days and 3.8 days, respectively [5,9,10].

Mean cumulative duration of oxygen therapy in the present study was 10±2.9 days. The mean duration of hospital stay in the present study was 11.3±2.7 days. It was found that the survivability of neonates increased after five days of sildenafil therapy.

In the present study, a significant improvement in oxygenation after sildenafil treatment was indicated by a significant reduction in OI from 35.3±8.6 to 13.2±2.1 (p-value <0.001), a reduction in SOPI from 3.6±0.3 to 1.5±0.2 (p-value <0.001), a reduction in FiO_2 (%) from 94.6±8.19 to 24.2±4.5 (p-value <0.001), an increase in PaO_2 (mmHg) from 52±5.6 to 72±3.4 (p-value <0.001), and an increase in SpO_2 (%) from 83.5±8.6 to 93.5±5.1 (p-value <0.001). The reduction of OI was more significant in post-hoc analysis after 24 to 48 hours from the start of treatment. In Sayed A and Bisheer N's study, the reduction of OI from 34.9±9.6 to 13±3.2 (p-value <0.001), an increase in PaO_2 (mmHg) from 42.4±13.5 to 78±11.5 (p-value <0.001), and a reduction in FiO_2 (%) from 1.0±0 to 0.3±0.06 (p-value <0.001) were noted [5]. The reduction of OI was more significant in post-hoc analysis after the 3rd and 4th doses of sildenafil, i.e., from

18-24 hours from the start of treatment. According to their study protocol, sildenafil was discontinued if the neonate received eight doses of sildenafil (maximum period of 42 hours after the first dose) or if OI decreased to <15, whichever was earlier, and they stopped giving sildenafil after that, irrespective of the clinical condition of the enrolled neonates.

In the present study, oral sildenafil produced no noticeable effect on blood pressure during the study period with the doses used. No significant difference in mean blood pressure between presildenafil and postsildenafil measurements was noted (p-value=0.54). In Prithviraj D et al., study and Sayed A and Bisheer N's study, oral sildenafil produced no noticeable effect on blood pressure during the study period with the doses used [3,5].

Limitation(s)

The present study has recruited a relatively small sample size. The study does not have a control group to compare the efficacy of the drug in neonates with PPHN. The present study did not follow-up on neonates with PPHN after their discharge from the NICU. Intravenous sildenafil has not been included in the study.

CONCLUSION(S)

Sildenafil is an effective drug for the treatment of PPHN in neonates with meconium aspiration syndrome and/or severe birth asphyxia, especially in a resource limited setting where facilities like iNO and ECMO are not available, as demonstrated in the present study. It is recommended to further study the effect of sildenafil in other etiologies of PPHN apart from meconium aspiration syndrome and severe birth asphyxia.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Paediatrics, BJ Medical College, Civil Hospital, Ahmedabad, Gujarat, India.
2. Professor and Head, Department of Paediatrics, BJ Medical College, Civil Hospital, Ahmedabad, Gujarat, India.
3. Assistant Professor, Department of Paediatrics, BJ Medical College, Civil Hospital, Ahmedabad, Gujarat, India.
4. Consultant Paediatrician, Department of Paediatrics, Community Health Centre, Sayla, Surendranagar, Gujarat, India.
5. Consultant Paediatrician, Department of Paediatrics, Shishu Clinic and Vatsalya Hospital, Jhansi, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Arif Vohra,
18/C, Firdos Nagar, Near Firdos Masjid, New Dhor Bazar Road, Danilimda, Ahmedabad-380028, Gujarat, India.
E-mail: arif8789@yahoo.com

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