INTRODUCTION
The PPHN reflects a disruption of the normal perinatal 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 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.

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 (SpO2), 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 (FiO2), 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 FiO2 (%) from 94.6±8.19 to 24.2±4.5 (p-value<0.001), an increase in Partial pressure of oxygen (PaO2) (mmHg) from 52±5.6 to 72±3.4 (p-value<0.001), and an increase in SpO2 (%) 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.
Study Procedure

Neonates with meconium aspiration syndrome and/or severe birth asphyxia with clinical signs of PPHN on examination (hypoxemia 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 SpO₂, OI, SOP, 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 ABGA 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 FiO₂ 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±9.9 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 by 3.6±0.3 to 1.5±0.2 (p-value<0.001), a reduction in FiO₂ (%) from 94.6±8.19 to 24.2±4.5 (p-value<0.001), an increase in PaO₂ (mmHg) from 52±5.6 to 72±3.4 (p-value<0.001), and an increase in SpO₂ (%) 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 SpO₂ 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 FiO₂ 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 post sildenafil measurements was noted (p-value = 0.54) [Table/Fig-4]. Hypotension was observed 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 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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. of neonates with PPHN (n=48)</th>
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<tbody>
<tr>
<td>Male to female ratio</td>
<td>1.4:1 (n=48) (28 males, 20 females)</td>
</tr>
<tr>
<td>Nutritional status, n (%)</td>
<td>AGA 32 (67%), SGA 16 (33%)</td>
</tr>
<tr>
<td>Co-morbid condition, n (%)</td>
<td>Severe birth asphyxia 20 (42%), Meconium aspiration syndrome 16 (33%), Meconium aspiration syndrome with severe birth asphyxia 12 (25%)</td>
</tr>
<tr>
<td>Mean±SD age of enrollment and starting sildenafil in study population</td>
<td>15.6±4.3 hours</td>
</tr>
<tr>
<td>Mean±SD age of echocardiography diagnosis (hours)</td>
<td>31.2±6.9 hours</td>
</tr>
<tr>
<td>Mean±SD dose of sildenafil in study population</td>
<td>6.8±0.7 mg/kg/day</td>
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<tr>
<td>Mean±SD duration of sildenafil therapy</td>
<td>6.8±3.2 days</td>
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<tr>
<td>Cumulative duration of oxygen therapy (days) (Mean±SD)</td>
<td>10.2±3.9 days</td>
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<tr>
<td>Mean±SD duration of mechanical ventilation</td>
<td>6.6±3.2 days</td>
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<tr>
<td>Mean±SD duration of hospital stay</td>
<td>11.3±2.7 days</td>
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*Table/Fig-1*: Baseline parameters.

AGA: Appropriate for gestational age; SGA: Small for gestational age.
In the present study, at the time of admission, the mean FiO₂ (%) requirement was 94.6±5.1, a mean PaO₂ (mmHg) was 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. In comparison, Steinhorn RH et al., reported a mean FiO₂ (%) of 88±1.6, a mean OI of 27.7±4.2, and a mean PaO₂ (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.

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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.

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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.

REFERENCES