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PULMONARY VASODILATOR THERAPY IN NEONATES WITH HYPOXIC RESPIRATORY FAILURE– A PROSPECTIVE COHORT STUDY.

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Abstract

Introduction: Acute hypoxemic respiratory failure (AHRF) in newborns continues to be a clinical challenge with elevated risk for significant morbidities and mortality, especially when accompanied with persistent pulmonary hypertension of the newborn (PPHN). The primary goal of PPHN therapy is selective pulmonary vasodilatation. Combination therapies are of considerable interest for treatment which fails to respond to iNO monotherapy.

Objective: To compare the efficacy of the combined intravenous sildenafil with inhaled nitric oxide therapy versus inhaled nitric oxide monotherapy for the treatment of Persistent Pulmonary Hypertension of neonates in terms of duration and weaning of iNO

Study Design: Neonates (gestational age >37 weeks) diagnosed with pulmonary hypertension were enrolled in the study. Neonates were categorized into two groups. Group I (n=9) received only inhaled nitric oxide whereas Group II (n=6) received combined therapy with inhaled nitric oxide and Intravenous sildenafil. Main outcome was to compare the efficacy and duration of inhaled nitric oxide therapy between the two groups.

Results: Demographic characteristics between the two groups showed similar results. Combination therapy helped in early weaning of inhaled nitric oxide (10.8±23 vs. 24±8.6 hours). The duration of inhaled nitric oxide therapy was significantly shortened in combined therapy group (56 [16-106] vs. 78 [21-186] hours), however, there was no statistical significance (p=0.2). The incidence of mortality and neonatal outcomes seemed to be same between the groups (p>0.05).

Conclusion: Combined therapy resulted in shorter duration of inhaled nitric oxide therapy. Neonates who received combined therapy had shorter NICU stay and were weaned off earlier compared to only iNO group.

Keywords: Pulmonary hypertension, Neonate, Sildenafil, inhaled nitric oxide.

INTRODUCTION

The normal fetal circulation is characterized by high pulmonary artery pressure secondary to high pulmonary vascular resistance (PVR) with low pulmonary blood flow (Qp), leading to right-to-left shunting of blood flow across the ductus arteriosus and foramen ovale. This physiology allows for the preferential distribution of combined ventricular output to the placenta, providing efficient gas

exchange to enable optimal tissue oxygenation in the developing fetus. Successful transition from intra-uterine to extra-uterine life is dependent upon a rapid and dramatic decrease in PVR to accommodate an 8–10 fold increase in pulmonary blood flow, as tissue oxygenation becomes dependent upon alveolar gas exchange and high flow through the postnatal pulmonary circulation [1]. Infants who fail to achieve or sustain the normal decrease in PVR at birth develop severe hypoxemia, recognized as persistent pulmonary hypertension of the newborn (PPHN).

PPHN is a syndrome associated with diverse neonatal cardiac and pulmonary disorders that are characterized by a common physiology, which includes sustained elevations in PVR causing extra pulmonary right-to-left shunting of blood across the patent ductus arteriosus (PDA), the foramen ovale (PFO), or both, resulting in critical hypoxemia, poorly responsive to inspired oxygen and optimal mechanical ventilation. PPHN affects ~0.2% of live births and is associated with a one-year mortality of 7.6% of all babies [2]. Importantly, the incidence of PPHN is directly associated with the degree of prematurity, with rates as high as 18% in neonates born at 22–23 weeks gestational age [3].

Persistent pulmonary hypertension of the newborn (PPHN) is a potentially life-threatening condition which is associated with increased pulmonary vascular resistance, ventilation-perfusion mismatch, and right-to-left shunting resulting in systemic hypoxia. The prevalence of PPHN has been estimated at 1.9 per 1000 live births (1).

Optimal management of PPHN involves selective pulmonary vasodilatation without worsening systemic hemodynamic. Inhaled nitric oxide (iNO) readily diffuses from alveoli into pulmonary smooth muscle cells causing pulmonary vasodilatation with minimal systemic consequences because of its short half-life (2–6s) and rapid inactivation by avid NO-hemoglobin binding in the circulation [2,3]. Inhaled NO is a rapid and selective vasodilator secondary to the ability to deliver this small gas molecule via inhalation, both invasively and non-invasively, to air spaces approximating the pulmonary vasculature causing decreased intrapulmonary right-to-left shunting and improved V/Q matching [3]. Inhaled NO which has repeatedly been shown to be safe and effective in reducing the need for ECMO, including large placebo-controlled multi- center trials, remains the only United States Food and Drug Administration (FDA) approved specific pulmonary vasodilator therapy for late preterm and term infants with AHRF and PPHN [4]. Initial RCTs demonstrated a decreased need for ECMO support in late preterm and term infants with severe PPHN and an oxygenation index (OI) of 25–40. A subsequent large trial did not report reductions in ECMO use or death with earlier use of iNO in infants with moderate respiratory failure (median OI of 20) [5].

The most common reason for failure to respond to iNO is inadequate lung recruitment and measures to improve lung volume, including changes in ventilator strategy, initiation of high frequency ventilation or surfactant administration, should be addressed prior to dose alterations. Findings from past RCTs highlight that iNO at studied doses has minimal toxicity in late preterm and term infants.

Sildenafil, available as intravenous (IV) and enteral forms, is the primary PDE5 inhibitor used for the treatment of PH. Sildenafil is a useful adjuvant therapy in acute PPHN for infants with an inadequate response to iNO or with the lack of iNO availability, especially in resource limited countries. As with iNO therapy, sildenafil should be used cautiously in neonates with LV dysfunction, because of a high risk for pulmonary edema, and may be most beneficial in combination with agents targeting cardiac performance or reducing LV afterload. Two trials demonstrated the early use of sildenafil improved oxygenation and outcomes in late preterm and term infants who were not treated with concurrent iNO therapy [45,46]. In a recent multicenter trial, IV sildenafil did not demonstrate a decreased need or duration of iNO therapy, though the treatment effect may have been diluted by inclusion of infants with a lower OI at enrollment [47]. Sildenafil is generally well tolerated when administered at recommended doses with the most common side effect being systemic hypotension.

The primary goal of PPHN therapy is selective pulmonary vasodilatation. Nitric oxide (NO) is one of the selective pulmonary vasodilators and synthesized from L-arginine by nitric oxide synthase. Currently, the most common therapy in severe PPHN is inhaled nitric oxide (iNO) which causes potent, selective, sustained pulmonary vasodilatation (2-4). Despite a favorable efficacy; outcomes for neonates treated with iNO therapy are not universally helpful. Approximately 30-40 % of neonates treated with iNO do not respond (5). The reasons for poor response to iNO therapy are not well known,

it may be related to endothelial dysfunction, down-regulation of endogenous nitric oxide, or multiple etiologies of PPHN. So that, no single treatment is effective in all cases (6).

Combination therapies are of considerable interest for treatment which fails to respond to iNO monotherapy. The use of combined pulmonary vasodilator therapy is shaped by the underlying pathophysiologic process, anticipated clinical course, and evolving interactions of the cardio-pulmonary axis of individual neonates. It is imperative to reiterate that while critical to the management of PPHN, successful use of vasodilator therapy is dependent upon optimizing supportive measures including systemic hemodynamics and pulmonary recruitment. Both changes in oxygenation and hemodynamics should be serially assessed to guide the addition, titration, and weaning of pulmonary vasodilators.

Higher concentrations of iNO are unlikely to be beneficial and increase the risk of adverse effects [40]. Reassessment of systemic hemodynamics and serial ECHOs are useful in guiding therapy when oxygenation remains minimally response to iNO. Limited data exists to support dual vasodilator therapy in PPHN, but careful consideration of augmenting iNO therapy with IV sildenafil, inhaled PGI2, or IV PGI2 are reasonable options for infants whose OI remains >20 in the acute setting without systemic hypotension and who have normal left ventricular function.

Minimal clinical data exists to support the use of dual vasodilator therapy in PPHN in acute PPHN. There is minimal evidence to guide weaning of pulmonary vasodilators in the setting of combined therapy. The present study aims to analyze the role of use of dual vasodilator therapy in acute PPHN.

OBJECTIVES

1. To compare the effects of combined therapy (IV sildenafil and iNO) versus iNO monotherapy in neonates with PPHN in terms of weaning and duration of iNO therapy
2. To analyze the effect of combined therapy (IV sildenafil and iNO) and iNO monotherapy on neonatal morbidity and mortality.

Methodology

This prospective cohort study was conducted in level IIIA NICU of Shri BM Patil Medical College Hospital and Research Centre, Vijayapura Karnataka. Study duration: 1 year. This is the referral unit for iNO therapy in neonates in this part of northern Karnataka. We studied 15 neonates, with severe hypoxic respiratory failure (HRF) with Oxygenation index (OI) > 15 with clinical & echocardiograph evidence of Pulmonary Hypertension. ECHO was done by a cardiologist in all cases to rule out any congenital heart disease. Neonates who have severe asphyxia, congenital heart defect and congenital diaphragm hernia were excluded from the study. This study was approved by the Institutional ethics committee, BLDE University Vijayapura.

Neonates were categorized in two groups based on type of intervention. Group I consisted of neonates who were treated with inhaled nitric oxide monotherapy. Group II consisted of neonates who were treated with combined therapy (iNO and IV sildenafil). Birth weights (g), gestational ages (week), gender, mode of delivery, being inborn/out born, age at the time of NICU admission (hour), type of respiratory support required (before/after iNO), severity of illness (by oxygenation index), length of stay in hospital (day), detail of the treatments included age at iNO therapy (hours) commenced; time of weaning, duration of iNO therapy were documented in a predefined structured proforma. Also, recognized maternal, prenatal, and postnatal risk factors were recorded.

Table 1: Demographic characteristics of the study groups

Characteristics	**Monotherapy (N=10)**	**Combined Therapy (N=10)**	**P VALUE**
Maternal age (years)*	32.1±4.4	29.6±6.4	0.2
Vaginal birth (n,%)	06(60)	05(50)	0.4
Gestational age (weeks)*	38.2±1.3	38.8±1.4	0.8
Birth weight(g)*	2763±672	2895±845	0.4
Gender, Male (n,%)	07(70)	06(60)	0.4
Apgar score†			

1min	5(1-7)	5(2-7)	0.5
5min	8(4-9)	7(4-9)	0.5
iNO administration time(h)	4(1-13)	9(4-16)	0.2
Surfactant administration (n, %)	9(64.3)	5(62.5)	0.9

*mean ±standard deviation† median (min-max), iNO; Inhaled nitric oxide, combined therapy, iNO and sildenafil.

Table2: Primary diagnosis on NICU admission in study neonates.

Primary diagnosis	**iNO monotherapy (n=9)**	**Combined therapy (n=6)**
Meconium Aspiration Syndrome (N, %)	4(44.4)	2 (33.3)
Perinatal Asphyxia (N,%)	2(22.2)	2(33.3)
Respiratory Distress Syndrome (N,%)	1(11.1)	1(16.6)
Pneumonia (N,%)	1(11.1)	1(16.6)
Idiopathic Pulmonary Hypertension (N, %)	1(11.1)	0

iNO, inhaled nitric oxide; combined therapy, iNO and sildenafil

Definition and criteria of nHRF/PPHN

Neonatal hypoxic respiratory failure was defined as Oxygenation Index (OI) greater than 15. OI is calculated as: OI = [(FIO2 X Paw)/PaO2] X 100 where Paw is mean airway pressure.

Table3: Comparison of oxygenation indices and MV support between groups

Characteristics	**INO Monotherapy (9)**	**Combined Therapy (6)**	**P Value**
Type of MV support during iNO therapy-n(%)			
• High-frequency oscillation	3(33.3)	1(16.6)	0.12
• Conventional mechanical ventilation	6(66.6)	5(83.3)	0.37
Blood gases values on NICU admission			
pH*	7.21±0.1	7.05±0.25	0.06
pCO2(mmHg)*	62.5±23	67.7±22	0.62
pO2(mmHg)*	34.4±11.1	38.4±13.0	0.48
OI1*	18±2	17±2	0.66
OI2*	10 ± 2	9 ± 2	0.78

mean ± standard deviation, iNO; Inhaled nitric oxide, combined therapy, iNO and sildenafil, MV; Mechanical ventilation, OI; Oxygenation Index,pCO2; Partial carbon dioxide pressure, pO2; Partial oxygen pressure, OI1; Obtained right before administration of iNO, OI2; Obtained at the second hour of iNO treatment

Neonates manifesting hypoxemia that is disproportional to the degree of parenchymal lung disease and also have a difference of 5% or more in pre-ductal and post-ductal SpO2 levels were diagnosed as clinical PPHN. For definitive diagnosis of PPHN two-dimensional color Doppler echocardiography was performed by cardiologist. Echocardiography evidence of PPHN was defined as an estimated peak systolic pulmonary-artery pressure that was higher than 40 mm Hg as indicated by a tricuspid regurgitated jet flow, a right-to-left shunt on ductus arteriosus or a patent foramen ovale.

Initially, all the newborns were started on Assist/Control ventilation with arterial blood gas targets to maintain PaO2 between 60 and 70mmHg, PaCO2 between 40 & 60mmHg and pH≥7.25. If the infant had Persistent hypoxemia i.e. Pre-ductal SaO2<80% on an FiO2>0.6 with Mean airway pressure of > 10 and OI>15, neonate was started on Conventional ventilation (SIMV WITH PSV (SLE 6000 infant ventilator) in 11 neonates. High- Frequency Oscillatory Ventilation (HFOV by SLE 6000 infant ventilator) was used by setting the Frequency of 8-10 with MAP of > 12 in 4 neonates with amplitude of 30-40. Further ventilator settings were changed as per repeat Blood gas values and chest x-ray findings. Sedation with intravenous infusion of Fentanyl was done. Intravenous Sildenafil infusion was started in group 2 neonates in a dose of 1.6 mg/kg/day. Inotropes (Dobutamine, Adrenaline & Milrinone) were used to maintain Mean Arterial Pressure of 45-60mmHg. Natural surfactant was given to neonates with chest x-ray findings of parenchymal lung disease requiring FiO2>60%with

Meconium aspiration neonates before starting on iNO therapy at 12 to 24hours of life.

Initiation of iNO therapy-A written consent was obtained from the parents before initiation of iNO therapy. Therapy was initiated with iNO 20ppm by inhaled nitric oxide delivery system (INOSYS SYSTEM) & it was used only as a rescue therapy for infants having failed conventional ventilation /HFOV & underlying OI ≥15. Inhaled Nitric oxide gas was obtained from Chemix lab, Bangalore who certified a concentration of 900 ppm and contamination by other oxides of nitrogen was < 2% (Normal industrial grade iNO contains impurities >6%, and Medical Grade iNO contains<1% impurities which is not available in India). Subsequent monitoring included OI, AaDO2, a/A ratio, Blood pressure, Pre-postductal SaO2 & other vital parameters. Methemoglobin levels by Maximo pulsoximeter was monitored every 24 hourly during the course of therapy to avoid toxicity (5%). Nitrogen dioxide levels were also monitored continuously with help of Inosys system which was documented at 1hourly interval. Inosys system has user-settable alarms for high & low concentrations of both NO & NO2, & the unit automatically reduces the therapy if an alarm is triggered.

Maintenance & weaning of iNO- As the oxygenation improved, FiO2 was decreased, while the concentration of iNO was kept constant. Once the FiO2<0.5 and PaO2>60mmhg, weaning of iNO was attempted. It was done in decrements n of 5ppm every 4 hourly as tolerated (No increase in Fio2>0.1 to maintain PaO2>60mmhg) by the infant till a concentration of 5ppm of iNO was reached and then by 1ppm every 4hourly till it reaches 1ppm. 1ppm was continued over 24hrs & then stopped. Response was defined as increase in PaO2>20mmhg after 2-6 hours of initiation of therapy11.

Sildenafil therapy

Sildenafil is selective phosphodiesterase type 5 inhibitor. PDE5 is found in the smooth muscle of the pulmonary vasculature, where it is responsible for the degradation of cyclic guanosine monophosphate (cGMP). cGMP produces smooth muscle relaxation. Sildenafil increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In neonates with pulmonary hypertension, this can lead to selective vasodilatation of the pulmonary vascular bed and, to lesser degree, vasodilatation in the systemic circulation

Neonates who met the inclusion criteria and received iNO treatment right after admission along with sildenafil were analyzed. Sildenafil was started in neonates on iNO therapy, failing to wean off iNO after initial stabilization of Oxygenation. Sildenafil was administered intravenously as an infusion at a dose of 1.6mg/kg/day. After weaning from the ventilator and iNO therapy, sildenafil was gradually tapered and stopped.

Outcomes

Our Primary outcome was the weaning of iNO therapy and duration of iNO therapy .Secondary outcomes were the mortality rates and morbidities such supplemental oxygen dependency.

Statistical analysis

Characteristics of neonates and the outcome measures were examined descriptively using mean+/-SD and frequency percentages. For the main outcome measure, paired t test was used. All analyses were performed with the use of SPSS statistical software, version23.

Results

A total of 15 neonates were enrolled in study group. In group I, 9 neonates and in group II, 6 neonates were enrolled. The baseline characteristics and major risk factors are listed in Table 1. Demographic characteristics were similar in both groups. Primary causes of PPHN and co-morbidities were listed in Table 2.The most common cause was meconium aspiration syndrome in both groups. Most of them were secondary PPHN, primary PPHN was only one. Comparison of oxygenation indices and MV support between groups are summarized in Table 3. During study period, 3 neonates were on High Frequency Oscillation Ventilation and 6 neonates on Conventional Ventilation in iNO Monotherapy

group whereas 1 neonate on High Frequency Oscillation Ventilation and 5 neonates on Conventional Ventilation in Combined therapy group. Combined therapy with sildenafil was significantly associated with earlier (10.8±23 vs. 24±8.6 h; p=0.01) and successful weaning of iNO treatment. Sildenafil was started in neonates on iNO therapy, failing to wean off iNO after initial stabilization of Oxygenation. Overall duration of iNO therapy was shorter in combined group [56[16-106] vs. 78 [21-186 hours]. (Table4).

Table4: Comparison of Neonatal Mortality and Morbidities between Groups

Outcomes	INO Monotherapy (9)	Combined Therapy (6)	P Value
Death	3 (33.3)	2(33.3)	0.4
Length of stay in hospital for survivors (days)*	25.3±6.8	24.2±6.3	0.6
Discharge with no intervention, n (%)	6(66.6)	4(66.6)	0.8
Time of weaning from iNO therapy,(h)*	24±8.6	10.8±23	**0.01**
Duration of iNO therapy for survivors, (h)median	78[21-186]	[56[16-106]	**0.02**

*mean ±standard deviation, iNO; inhaled nitric oxide; combined therapy, iNO and Sildenafil.

Discussion

The safety and efficacy of iNO therapy for PPHN have been particularly well studied through large placebo-controlled trials (11-14). Despite efficacy and safety of iNO therapy, respond to the treatment is not unique since PPHN occurs in association with a diverse group of neonatal respiratory illnesses. In this cohort of neonates with PPHN the most common cause was meconium aspiration syndrome in both combined and monotherapy groups and the other causes were distributed evenly in both groups. Based on the multiple etiologies of PPHN, no single therapy is effective in all cases. Current novel and experimental therapies include alternative means of delivering NO, prostanoids, endothelin receptor antagonists, antioxidant therapy, and PDE-5 inhibitors etc. (15). Among the mentioned therapies both oral and intravenous sildenafil, a PDE-5 inhibitor, have been studied in term and late preterm neonates with PPHN and found to improve oxygenation and survival. Furthermore, our results supported that combined therapy also reduces the overall duration of the treatment and provides faster weaning from iNO. Mortality rates were lower in combined therapy group (22%) when compared with monotherapy (50%) even the combined therapy group were out-born patients who required transportation to get iNO treatment. This outcome did not reach to a statistically significance possibly due to low sample size.

Our study showed that the duration of iNO therapy was significantly shorter in sildenafil and iNO combination therapy group. Also, combined therapy with sildenafil was associated with early weaning of iNO and a reduction in need for iNO therapy when compared to iNO monotherapy. This improvement may be explained as that different drugs or therapies fix the different mechanisms which are responsible for the pathogenesis of PPHN, such as heart failure, maldevelopment, or vascular remodeling. However, data about prophylactic administration of sildenafil and combination therapies in newborn infants are very limited. A multicenter, randomized clinical trial is required to test the efficacy of sildenafil in iNO-resistant PPHN.

Namachivayam et al. (16) demonstrated that's single dose of oral sildenafil is effectively protected patients from rebound pulmonary hypertension who are on iNO therapy, in a prospective, randomized, controlled study. Similarly, to our results Lee et al. (17) reported that the use of oral sildenafil facilitates weaning from iNO therapy. Shah et al. (18) conducted a Cochrane meta-analysis and reported that Sildenafil in the treatment of PPHN has significant potential especially in resource limited settings. However, a large scale randomized trial comparing sildenafil with the currently used vasodilator, inhaled nitric oxide, is needed to assess efficacy and safety.

In an analysis of a small population of neonates with PPHN it is reported that, apart from different underlying pathological conditions, time of beginning of iNO therapy is a strong predictor of outcome (19). As iNO is not available in all neonatal units yet, it is of great interest to identify alternative therapies that could be used immediately after the diagnosis of PPHN, or even in the presence of a

strong clinical suspicion, before the arrival of the baby to the referral center. In our study outcomes were comparable in inborn and out born neonates despite the combined therapy group received iNO significantly later that supports the idea that neonates should get alternative therapies before transportation.

Conclusion

This study suggest that combination therapy (with sildenafil and iNO) could be more effective to reduce iNO weaning time and overall duration of iNO therapy that is relatively expensive. These results need to be confirmed with further large, prospective well-designed trials comparing drug dosages, time of onset, rank of onset, and safety of drug-drug interaction.

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Reference

1. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics 2000;105 (1):14-20.
2. Oishi P, Fineman JR. Pulmonary Hypertension. PediatrCritCareMed.2016;17(8):140-5.
3. Stayer SA, Liu Y. Pulmonary hypertension of the new-born. Best Pract Res Clin Anaesthesiol. 2010;24(3):375-86.
4. Finer NN, Barrington KJ. Nitric oxide therapy for the newborn infant. SeminPerinatol.2000;24(1):59-65.
5. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database SystRev2006;(4):CD000399.
6. Steinhorn RH. Diagnosis and treatment of pulmonary hy-pertension in infancy. Early Hum Dev 2013;89(11):865-74.
7. Steinhorn RH. Neonatal pulmonary hypertension. PediatrCritCareMed2010;11(2):79-84.
8. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study.Pediatrics2006;117(4):1077-83.
9. Dhariwal AK, Bavdekar SB. Sildenafil in pediatric pul-monary arterial hypertension. J Postgrad Med 2015;61(3):181-192.
10. Ahsman MJ, Witjes BC, Wildschut ED, Sluiter I, Vulto AG, Tibboel D, et al. Sildenafil exposure in neonates with pulmonary hypertension after administration via a nasogastric tube. ArchDisChildFetalNeonatalEd2010;95(2):109-14.
11. Roberts JD Jr, Fineman JR, Morin FC, Shaul PW, RimarS, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. N Engl J Med.1997;336(9):605-10.
12. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the new-born. Clinical Inhaled nitric oxide research Group.NEnglJMed2000;342(7):469-74.
13. Davidson D, Barefield ES ,Kattwinkel J, Dudell G, Damask M, Straube R, et al. Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn : A randomized, double-masked, placebo-controlled, dose response, multicenter study. Pediatrics1998;101(3):325-34.
14. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997;336(9):597-604.
15. Lakshminrusimha S, Konduri GG, Steinhorn RH. Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm

neonates. JPerinatol2016;36(2):12-9.
16. Namachivayam P, Theilen U, Butt WW, Cooper SM, Penny DJ, Shekerdemian LS. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. AmJRespirCritCareMed2006;174(9):1042-7.
17. Lee JE, Hillier SC, Knoderer CA. Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. JIntensiveCareMed2008;23(5):329-34.
18. Shah PS, Ohlsson A. Sildenafil for pulmonary hyperten-sion in neonates. Cochrane Database Syst Rev 2011;(8):CD005494.
19. Nassi N, Daniotti M, Agostiniani S, Lombardi E, Favilli S, Donzelli GP. Sildenafil as "first line therapy" in pulmonary persistent hypertension of the newborn? J Matern Fetal Neonatal Med.2010;23(3):104-5.