Caracteristics, Diagnosis, Management and Output of Persistent Pulmonary Hypertension of the Newborn at Dr. Soetomo Hospital

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Abstract

Background Persistent pulmonary hypertension of the new-born (PPHN) is a failure of lung circulation in new-born. However the data related the characteristics of clinical profile, diagnostic, management and the outcome was still limited.

Objective To investigated the characteristics, diagnostics, management and outcome from PPHN.

Methods Retrospective observational study. Neonates with PPHN from January 2015 to December 2019 were identified from medical record. After the data was excluded, the characteristics, diagnostic, management and the outcome was collected. The statistical analysis to known the frequency and the chi-square test used to analyse the association between the treatment and the outcomes ($P < 0.05$).

Results 37 medical records enrolled the study, with the characteristics; 62.2% babies was boy, 70.3% with term infant, 70.3% with normal birth weight, 24.3% with maternal history of eclampsia. 62.2% babies born by C-section, 21.9% with history of asphyxia and MAS. 78.4% with differences between pre- and post-ductal saturation. From echocardiography result, 13.5% diagnosed as mild PPHN, 54.1% as moderate PPHN and 32.4% severe PPHN. From the management consisted of 5.4% with O_2 nasal, 32.4% O_2 CPAP and 62.2% O_2 ventilator, 24.3% with sildenafil, 5.4% with combination sildenafil and illoprost, 5.4% with combination sildenafil, illoprost, and surfactant, 2.7% with combination sildenafil, illoprost, surfactant, and inotropic, 24.3% with combination sildenafil, illoprost, and inotropic, and 37.8% with combination sildenafil and inotropic. The outcomes was obtained 35.1% babies was died and 64.9% babies was cured, with oxygenation supplementation had significantly affecting the outcomes (P=0.02)

Conclusion The characteristics of PPHN was dominated by baby boy, term infant and good birth weight, history of asphyxia and MAS, maternal history of eclampsia, C-section delivery and the differences between pre- and post-ductal saturation. The diagnosis commonly with moderate PPHN. The management with O_2 ventilator and combination sildenafil-inotropic. The outcome mostly the babies was cured.

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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome lung circulation failure to transition from fetal circulation to neonatal circulation.

The incident PPHN is quite rare, in worldwide ranging from 1-6 over 1000 of live births. Based on medical record from 2015 to 2016 In Dr. Soetomo Hospital were found 20 cases. This condition generally life-threatening with the prognosis tends to be poor, especially in developing countries[1,5,14,22]. Samudro and Mulyadi (2012) in their study explained, PPHN with the delivery history followed with low birth weight, presence of infection, and labor procedures with C-section, tends to have a poor prognosis. However, the data in Indonesia is still incomplete[20].

In the world the mortality rate infants with PPHN is around 10% and will increases if followed by congenital anomaly such as diaphragmatic hernias. For the morbidity rate it was around 25% consist of developmental disorders, pulmonary hypertension and neurological disorders[1].

Walsh-Sukys MC (2000), infant with PPHN have several clinical profile characteristics, commonly happened in baby boy and white race ethnic[23]. Another clinical profile that PPHN could presence in parenchymal lung disease in the newborns, include of meconeal aspiration syndrome (MAS) and or respiratory distress syndrome (RDS). That is the reason why PPHN could occur in preterm or term infants [8,20]. In addition, characteristic of infant with history of intrauterine growth restriction (IUGR), hypoglycemia, polycythemia, or oligohydramnios are also suspected as the risk factors of PPHN [2,20].

Diagnosing PPHN is not easy, sometimes it can underdiagnosed and considered a congenital heart disease (CHD), so the close initial evaluation is needed especially in infants with history born with hypoxia. Characteristic of maternal history also important, because mother with diabetes, asthma, hypertension, eclampsia, obesity and drug used during pregnancy was suspected as a risk factor, history of delivery, physical examination by measure the pre- and post-ductal oxygen saturation also important to know. As the gold standard to diagnosed PPHN, echocardiography still preferred. With echocardiography examination we can found the anatomical disorder and also to monitor the effectiveness of the therapy was given [9].

After the diagnosed already established, the therapy for PPHN will be given based on the severity. The goal of the PPHN management are to overcoming circulatory failure and improving oxygenation needed. However, in Dr, Soetomo Hospital there were known several combinations therapy and the clear data about the right combination therapy in order to obtain the best outcome is still unknown. Management therapy at Dr. Soetomo Hospital currently includes many combination therapy consist of oxygenation suplementation, with surfactants, or vasorelaxants, or phosphodiesterase inhibitors, or illoprost inhalation and or inotropes administration[1, 13,19,20,22]. Therefore, to obtain a good outcome babies with PPHN, the proper diagnosis and good management evaluation are needed to achieve optimal conditions [1,19].

The aimed of this study to investigated the characteristics of clinical profile, diagnostics, management and outcome from PPHN.

Material and Methods

A retrospective observational study, with the neonates who diagnosed as PPHN that hospitalize in NICU room and the data was collected based on medical records. The data was collected from January 2015 to December 2019. The inclusion criteria for the medical record consist of the infants with aged since birth to 30 days old and already diagnosed as PPHN, confirmed by echocardiography, then got management therapy according to applicable guidelines.The statistical analysis was to calculate the frequency (by presentation) and the chi-square test used to analyse the association between the treatment and the outcomes ($P < 0.05$).

Operational Definition

Persistent pulmonary hypertension of new-born defined as increased pulmonary vascular resistance in neonates characterized respiratory distress, followed by shunting of blood circulation from the right to the left heart chamber with clinical severe hypoxemia [16], and already confirmed by *echocardiography* [18].

The characteristics PPHN are clinical profile included sex and the risk factors during gestational-age, infant birth weight, history of delivery, maternal history (eclampsia, premature rupture of membranes (PRoM), oligohydramnios, bleeding during pregnancy, and history of drugs consumption), history of labor procedure (spontaneous or C-section), history of natal

(RDS, asphyxia, MAS, congenital heart disease, HIE and diaphragmatic hernia), and complications during hospitalization.

The diagnosis of PPHN in infants based on clinical symptom with respiratory distress followed by hypoxia that occurs in the first 6-12 hours after birth and the history of risk factors PPHN [8], from physical examination with differences more 10% between pre- and post-ductal saturation , confirmed with echocardiography. From echocardiography result of shunting from right to left through *patent ductus arteriosus* (PDA) and or *patent foramen ovale* (PFO), increased right ventricular pressure and pulmonary artery pressure with tricuspid regurgitation (TR), or found right ventricular dysfunction [16,18]. The severity of PPHN are divided into mild PPHN (echo result mild TR), moderate PPHN (moderate TR) and severe PPHN (severe TR) [10].

The management therapy of PPHN included oxygenation (administration through nasal canul / CPAP / mechanical ventilator) and drug administration (sildenafil; sildenafil with illoprost; sildenafil, illoprost, and surfactant; sildenafil, illoprost, surfactant and inotropic; sildenafil, illoprost and inotropic; and sildenafil with inotropic). The purpose of management to increase oxygen supply, reduce oxygen demand, facilitate adequate gas exchange in the lungs, reduce pulmonary vascular pressure by increasing vasodilation of pulmonary blood vessels, improving mixing of flow in the cardiac atrium and through PDA and improving metabolic disorders [15,18].

The outcome of PPHN after evaluation and treatment defined as recovery (without sequelae or with sequelae) or died [4].

Results

In this study, were found 56 medical records infants with PPHN, but only 37 medical record still remained. The characteristics in this study based on sex 62.2% dominated with baby boy with a boy to girl ratio was 1.6 : 1. Based on the maternal history in this study consisted of 24.3% with eclampsia, 18.9% with PRoM, 13.5% with oligohydramnios, 5.4% with bleeding during pregnancy, 70.3% with appropriate gestational age consisting of term-infant 70.3% and preterm infants 29.7%. Based on the history of childbirth 62.2% babies were born with C-section and 37.8% were born spontaneously, and according to birth weight 70.3% with normal birth weight, 24.3% infants with low birth weight and infants with very low birth weight (5.4%) (Table I).

The characteristic of perinatal history, there were 21.6% infants with asphyxia neonatorum, 21.6% with MAS, 10.8% with RDS, 5.4% with hypoxic ischemic encephalopathy (HIE), 2.4% with diaphragmatic hernia and 2.7% with congenital heart disease. The complications during hospitalization consist of pneumonia (45.9%), and sepsis (43.2%), with length of stay about 10 days.

Table II showed the diagnostic from babies with PPHN based on differences between pre- and post-ductal saturation, confirmed with echocardiography as the gold standard diagnostic. From this study was found 78.4% with the differences between pre- and post-ductal saturation and from echocardiography was confirmed 13.5% with mild PPHN, 54.1% with moderate PPHN dan 32.4% with severe PPHN.

Table I. The characteristics persistent pulmonary hypertension od the newborn

Characteristics	Category	n (n=37)	%
Sex	Boy Girl	23 14	62.2 37.8
Maternal history	Eclamsia PRoM Oligohydramnion Bleeding during pregnancy Gestasional age : Term infant Preterm infant	9 7 5 2 26 11	24.3 18.9 13.5 5.4 70.3 29.7
Delivery history	C-Section Spontaneus Birth weight : Normal birth weight Low birth weight Very low birth weight Extremely low birth weight	23 14 26 9 2 0	62.2 37.8 70.3 24.3 5.4 0.0
Perinatal history	Asphyxia MAS RDS	8 8 4	21.6 21.6 10.8
	HIE Diafragmatic Hernia CHD	2 2 1	5.4 5.4 2.7
Complication	Pneumonia	17	45.9
	Sepsis	16	43.2
Length of stay (days) Mean (min-max)		10 days (2-18 days)	

Table II. Diagnostic confirmation of PPHN

Diagnostic resul	Category	Total (n)	%
The differences between pre- and post-ductal saturation	Yes No	29 8	78.4 21.6
Echocardiography	Mild PPHN Moderate PPHN Serevere PPHN	5 20 12	13.5 54.1 32.4

Table III showed the management for PPHN consist of oxygenation supplementation and drug combination therapy. In this study was found 5.4% was got O_2 nasal, 32.4% with O_2 CPAP and 62.2% with mechanical ventilator support. For drug combination therapy was found 24.3% was got sildenafil, 5.45 with combination of sildenafil and illoprost, 5.4% with combination of sildenafil, illoprost, and surfactant, 2.7% with combination of sildenafil, illoprost, surfactant, and inotropic, 24.3% with combination of sildenafil, illoprost, and inotropic and 37.8% with combination of sildenafil and inotropic.

Table III. The management therapy of PPHN

Therapy	Total (n)	%
· Oxygenation		
O2 nasal	2	5.4
O2 CPAP	12	32.4
Mecanical ventilator	23	62.2
· Sildenafil	9	24.3
· Sildenafil + Illoprost	2	5.4
· Sildenafil + Illoprost + surfactant	2	5.4
· Sildenafil + Illoprost + surfactant + Inotropic	1	2.7
· Sildenafil + Illoprost + Inotropic	9	24.3
· Sildenafil + Inotropic	14	37.8

Table IV showed the outcome of PPHN based on the diagnostic from echocardiography. In this study was found 64.9% PPHN cured which are 13.5% with mild PPHN, 45.9% with moderate PPHN and 5.4% with severe PPHN. 35,1% PPHN was died, which are 8.1% with moderate PPHN and 27% with severe PPHN.

Table IV. The outcome of PPHN related to the diagnostic result

Outcome	Mild PPHN n (%)	Moderate PPHN n (%)	Severe PPHN n (%)	Total n (%)
· Cured	5 (13.5)	17 (45.9)	2 (5.4)	24 (64.9)
· Died	0 (0.0)	3 (8.1)	10 (27.0)	13(35.1)

Table V to show association between the outcome to the management and to the complication. In this study was found oxygenation support have significant association with the outcome of PPHN ($P < 0.05$).

Tabel V. Bivariant analysis of PPHN

Management therapy	Cured	Died	P
	n (%)	n (%)	
· Sildenafil	9 (24.3)	0 (0.0)	0.052*
· Sildenafil + Illoprost	2 (5.4)	0 (0.0)	
· Sildenafil + Illoprost + surfactant	1 (2.7)	1 (2.7)	
· Sildenafil + Illoprost + surfactant + Inotropic	0 (0.0)	1 (2.2)	
· Sildenafil + Illoprost + Inotropic	6 (16.2)	3 (8.1)	
· Sildenafil + Inotropic	6 (16.2)	8 (21.6)	
Oxygenation :			0.02*
O2 nasal	2 (5.4)	0 (0.0)	
O2 CPAP	12 (32.4)	0 (0.0)	
Mechanical ventilator	10 (27.0)	13 (35.1)	
Complication			0.189*
· Sepsis	11 (29.7)	5 (13.5)	
· Pneumonia	9 (24.3)	8 (21.6)	

*Chi-square tes

Discussion

Research on persistent pulmonary hypertension of the newborn (PPHN) has been widely carried out, but the results obtained are still unsatisfactory. The occurrence of pulmonary vascular disorders in infants is known to be the cause of PPHN. Based on the pathophysiology, the disorder is divided into three, namely under-development of pulmonary vascularization during the intrauterine period, the presence of mal-development (abnormalities of the vascular structure), and or the presence of maladaptation (generally due to vascular spasm triggered by perinatal hypoxia). Currently, several characteristics was thought to be the predisposing factors for PPHN have been identified [21]. In this study, the characteristics of PPHN based on gender 62.2% was boy and 37.8% girls with a ratio of 1.6: 1. Choudhary's (2015) in his study, baby boy were also dominated 65% from all sample, as well as in Harish and Kamalarathnam's (2018), where the ratio of between boy and girl was 1.5: 1 [2,5].

The characteristic of PPHN based on maternal history, in this study was found 24.3% with eclampsia, 18.9% with history of premature rupture of membranes (PRoM), 13.5% oligohydramnion and 5.4% with placenta previa. Eclampsia and bleeding during pregnancy caused intrauterine hypoxia due to reduced oxygen supply that was distributed to the foetus. It will exacerbate the pulmonary transition process as a risk of developing PPHN that occurs when the baby was born. Bleeding during pregnancy will also cause foetal anemia, it will lead into the abnormalities pulmonary vascularization development (known as mal-development). The mother's condition followed by PRoM can cause pulmonary hypoplasia in infants as the results from oligohydramnios that occur during PRoM progress. It will lead to the abnormalities in parenchyma and the development of the pulmonary vascular. It also will decrease the number of blood volume and trigger vasoconstriction of pulmonary blood vessels. This process is known as underdevelopment that can caused PPHN [18]. For management this condition required generally prolonged cardio-respiratory support because sometime not responding to vasodilators administration [6,8]. Gestational age also known as the characteristic of PPHN. In this study, PPHN 70.3% occurred at term infant compared to babies born preterm. Research by

Roofthooft (2011) found PPHN occurred mostly at term infant than preterm infant. Harish S and Kamalarathnam C (2018), also showed 82.3% of PPHN occurred in term infant [5, 18]. The characteristics of the gestational age babies with PPHN in each health care facility can be different. The preterm babies, generally all the organs in an under-development condition, especially the lung. The under-development of the lungs will trigger hypoxia that in long term could be the risk factor of chronic lung disease as the secondary cause of PPHN. It will be worsen if followed by high pulmonary vascular resistance (PVR) due to failure of the post-natal transition [6]. In term infants the mechanism of PPHN is quite different, it due to maladaptation of the pulmonary parenchyma (eg, in MAS or RDS conditions) that also caused high PVR during the post natal transition[18].

The history of labor, included the procedure of delivery and the birth weight also known as the characteristic of PPHN. In this study 62.2% PPHN was found in C-section compared to spontaneous delivery was only 37.8%. Choudhary et al (2015), 57.89% PPHN found in babies who`s born by C-section, as well as in research of Harish S and Kamalarathnam C (2018), the incidence of PPHN in babies with history of C-section about 68.9% [2, 5]. PPHN in infants who`s born by C-section is caused by the interference of endogenous catecholamine secretion. Endogenous catecholamine in infants are important during the transition process. Disruption of it caused delayed the transition process, and also trigger exchange disorders in the lungs due to the lack of stimulation of the lung and significantly triggers immaturity of the lungs. The differentiated with spontaneous delivery can provide mechanical stimulation in the form of manual compression on the chest wall and stimulates the baby to breathe, also helps to expelling amniotic fluid in the respiratory track. However, this does not conclude that C-section is prohibited, because there are several indications that require the procedure to be performed [2, 4, 5].

In this study, PPHN occurred in 70.3% babies with normal birth weight, then low birth weight. Harish S and Kamalarathnam C (2018) found, 68.5% incidence PPHN happened in babies with moderate birth weight compared to babies with low birth weight [5]. PPHN in sufficient birth weight occurs due to secondary factors that cause maladaptation of the lung (babies born with MAS or transient tachypnea of newborn). But it didn`t mean PPHN couldn`t occurred in low birth weight infant, it just happen due to the under-development of the lungs tissues and vascularisation. The PPHN in low birth weight that identical to intrauterine growth retardation (IUGR), was caused by under-development mechanism of the lung. So, the infants with sufficient birth weight or less, each of them has the possibility to suffer PPHN [18, 21].

The perinatal history related to PPHN, in this study was found that neonatal asphyxia and MAS had the same incidence of PPHN (21.6%), followed by RDS, hypoxic ischemic encephalopathy (HIE), diaphragmatic hernia and congenital heart disease. Other characteristics are complications that occur during the hospitalization. The complications in our study consist of pneumonia (45.9%) and sepsis (43.2%). Sharma (2011), PPHN most often occurs in infants with a history of asphyxia and MAS because clinical hypoxia which can trigger pulmonary vascular spasm[21]. In the normal physiological condition, the air exchange process was done by placenta would be replaced by the lung, after the baby born, followed by increased of pulmonary oxygenation through complex biochemical mechanisms and processes. This will facilitate the transition process from the new born, but if it got disruption it will lead to failure of pulmonary development as well as vascular dysfunction. The mechanism known as maladaptation [24].

Roofthooft et al (2011) in their research, as addition infections (pneumonia, and or sepsis), congenital disorders such as diaphragmatic hernia and congenital heart disease can cause PPHN [5, 18]. These factors caused maladaptation of pulmonary development [18]. In addition, there was other mechanisms that could trigger PPHN due to abnormalities in the development of pulmonary vascularization (maldevelopment) which are generally idiopathic, for example in chronic foetal hypoxia, foetal anemia, or with congenital heart disease (PDA). The third mechanism that can trigger PPHN is the underdevelopment mechanism, for example in the condition of lung hypoplasia that occurs in infants with diaphragmatic hernias and infants with infections [18]. Infection is a risk factor of sepsis, as well as pneumonia. Infection will cause damage of lung parenchyma through surfactant inactivation mechanisms, release of pro-inflammatory mediators, and other chemical

reactions that increase the secretion of vasoconstrictors such as endothelin and thromboxane. If the condition is exacerbated by hypoxaemia that occurs since birth, it will aggravate vasoconstriction of the pulmonary vascular. On the other hand, if the sepsis not resolved, will decrease the systemic vascular resistance (SVR) with clinical hypotension. If the condition followed by an increase in PVR, it will be trigger shuting via from the right to the left heart and made the PPHN more severe [12]. Konduri and Kim (2009) explained that sepsis in PPHN was caused by infection with Group B Streptococcus and gram-negative organisms that acquired during hospitalization. The bacterial endotoxin released in the bloodstream caused pulmonary hypertension, these mechanisms made thromboxane, endothelin and cytokines release and the over-activation of nitric oxide. It also cause worst effect such as multi-organ failure including myocardial dysfunction [8].

Diagnosis of PPHN is not easy, from history taking of maternal and childbirth followed by a physical examination, supporting the diagnosis to detect PVR which is the characteristic of PPHN, as well as to find the condition of blood flow and myocardial function. Supportive non-invasive examinations are recommended PPHN. The recommendations suggest the pre- and post-ductal ratio of oxygen saturation (SpO_2) and echocardiography as the gold standard. From saturation that showed 5-10% difference between the right upper limb (pre-ductal) and the lower left (post-ductal) limb indicated the PPHN, but the disadvantages of this examination is unable to confirm heart structural abnormalities [6, 21]. This saturation measurement was carried out during the first 6-24 hours of life, after clinical signs of hypoxia were found. This examination is very helpful as the initial screening of PPHN, especially in limited health facilities before confirmed by echocardiography [8, 16, 17]. In this study, it was found that 78.4% of the newborn with differences of pre- and post-ductal saturation and 21.6% were not have it. The difference in pre- and post-ductal saturation in PPHN infants occurs due to episodic changes in circulating pulmonary blood flow and shunting from the right to the left heart chamber. If the changes of pulmonary circulation occur more intense, it mean the condition developed severely [12].

Echocardiography still recommended by 95% of respondents as the gold standard to diagnosed PPHN. This examination is easy to use and can be done bedside if the patient's condition was unstable. This examination is also used to assess progressivity or how the response of therapy that has been given [6]. Echocardiography used to determine the cardiac structural abnormalities and to rule out the differential diagnosis as cyanotic CHD, because from the physical examination, both of it can followed by systolic murmurs due to tricuspid regurgitation or continuous murmurs from PDA [8]. From echocardiography we can diagnosed PPHN if there was right ventricular hypertrophy, deviation of the interventricular septum to the left side, tricuspid regurgitation (TR), and right to left bidirectional shunting via PFO and PDA [12]. In this study was found, from echocardiography 13.5% patient with mild PPHN, 54.1% with moderate PPHN, and 32.4% with severe PPHN.

Oxygenation herapy in this study was found 5.4% infants received nasal O_2 therapy, 32.4% infants received O_2 CPAP and 62.2% with mecanical ventilator. The purpose of oxygenation management is to fix hypoxemia and improve the blood pressure, which it will effect reduction of the heart shunting from the defect [1]. If the condition followed by persistent hypoxia, with clinical possibility of PPHN, then the first step is to provide oxygenation until the diagnosis of PPHN has been confirmed [2]. Oxygen supplementation acts as a potent vasodilator and to assist post-natal physiological adaptation processes based on oxygen needs. However, during the oxygenation therapy it important to monitoring and choose the right way to give the oxygenation according to the severity so the oxidative stress could be prevented. Because if oxidative stress occurs, it will form reactive oxygen species which cause the opposite effect (vascular vasoconstriction) [16].

The management of PPHN, in this study consisted 24.3% patient got a sildenafil administration, 5.4% received a combination of sildenafil and illoprost, 5.4% received a combination of sildenafil, illoprost, and surfactant, 2.7% received a combination of sildenafil, illoprost, surfactant and inotropic, 24.3% received a combination of sildenafil, illopros, and inotropic and 37.8% infants received sildenafil and inotropic combination. Indication of therapy based on the clinical condition of patient and

the availability of the therapy in dealing with PPHN in each hospital. In this study, sildenafil commonly used in all infants especially with mild to severe PPHN. Sildenafil known as a phosphodiesterase inhibitor type 5 (PDE5) which selectively to reduce PVR and increase cyclic guanosinemonophosphate (cGMP), it cause a vasodilating effect the vascular. If the administration of sildenafil was combine with oxygen supplementation, it will give improvement and oxygenation needs [25].

Surfactant in PPHN especially indicated for infants with a history of MAS. Physiologically 5% -24% of the newborn can experience meconium staining of amniotic fluid (MSAF), 5% of this MSAF could develops into MAS and caused hypoxemia due to obstruction of the airway and surfactant inactivation [14]. Surfactant administration in the newborn will expected to stimulate the release of meconium from the airways, improve lung oxygenation and reduce shunting flow from the right to the left heart [14, 19].

The other recommended therapy in management of PPHN is the administration of vasorelaxants, which namely as illoprost. Vasorelaxants act by inhibiting the transport of calcium ions in lung and systemic vascular smooth muscle cells. The effect is to reduce vasoconstriction of blood vessels, but during the administration it needs to be monitored closely because can make systemic side effect in the form of hypotension. Illoprost can be given by inhalation especially in PPHN with severe hypoxia suspected caused by unclear cyanotic heart disease. When it got combined with sildenafil will give better results [1, 19]. In PPHN with clinical symptom persistent hypoxemic and hypotension. We could suspected increased of shunting right to left shunt was occur. Hypotension caused by systemic vascular resistance (SVR) was decrease and followed with increased shunting form. Inotropic agents is one of the methods to reduce the shunting, but depends to considerably in each health care facility, because there is no clear evidence which group is the best. Nakwan (2016), said the inotropes dopamine was choose as the first-line therapies, dobutamine and epinephrine will be selected as the second and third line therapies [16].

The outcome in this study was found that 24 patient was recovered, which 37.8% infants cured without sequelae, and 13 patient was died. The outcome of the patient who died especially in limited health care facilities tended to be high. Harish and Kamalarathnam (2018), in their study in India, said that the mortality rate of PPHN could reached 42.3% even though these babies had received sildenafil therapy and mechanical ventilators. Harish and Kamalarathnam (2018) suspect that the cause of death is due to inappropriate therapy. Ideally, oxygenation therapy should be accompanied by iNO (inhaled nitric oxide) or using the HFO (high frequency oscillation) or ECMO (extracorporeal membrane oxygenation) method. The obstacle is, the modality of the therapy is expensive and requires inexpensive technicalities [4, 5, 7]. iNO known has the fast effect and selective working site at pulmonary vascular (Luecke and Mcpherson., 2017). This mechanism caused vasodilator by involves the production of cyclic guanosine monophosphate (cGMP) in the muscularis lining of blood vessels, then it will activates cGMP kinase and causes calcium pump inhibitors in blood vessels. Decrease of calcium ions that enter the smooth muscle cells will trigger relaxation and vasodilation of pulmonary blood vessels. If the therapy combined with sildenafil, the effect of suppression of cGMP regulation will be prevented and the vasodilation can have a long half-time [26]. The other mechanism of iNO is to preventing anaerobic metabolism during hypoxia, by changes the hemoglobin binding that effect oxygenation supply improved [27]. The ECMO and HFO ventilation also can provide improvement for the lung oxygenation up to 53%, compared to regular mechanical ventilation in PPHN infants, with recovery rates from 81-82% [11, 27]. The combination of HFO and iNO also give the advantage, because with low pressure it can quickly corrected arterial oxygenation saturation [1, 3].

In this study, the oxygenation supplementation had a significant effect to the outcomes. Oxygenation is the first line therapy which acts as a major stimulant of the nitric oxide and prostacyclin pathways of the pulmonary vasodilator cascade. The advantage from oxygenation to PPHN are fast action and selective onset as a vasodilator for pulmonary vascularization and provides negative feedback to vasoconstriction stimulation in the central nervous system [27]. This oxygen supplementation can be adjusted based on mild to severe PPHN condition, for example in mild PPHN oxygenation can be given using a nasal cannula, followed by closed monitoring to the response as a consideration whether it is necessary

to increase the oxygen supplementation or not [14,19]. In this study, it was also known that nine babies received sildenafil without combined with other therapies, with the good outcome. The reason are, it depends on the severity of PPHN itself and as the sample if the baby's was suffered from mild to moderate PPHN. The severe PPHN mostly tends to give a poor outcome due to the maladaptation and mal-development processes that aggravate the condition, thus condition will needing a therapy including illoprost, surfactants and inotropes [18].

Complications during hospitalization suspected can effecting the outcome babies with PPHN. In this study were seen, 13.5% of PPHN infants died followed by sepsis and 21.6% followed by pneumonia. But, even though both of it have a fairly high incidence but there was no association with the outcome. Sepsis and pneumonia can cause high mortality and morbidity in PPHN, but it needs other circumstances conditions such as condition during pregnancy, labor history or perinatal history that could influenced the outcome [12, 18].

The aim of this study are to become the reference for further research which can be experimental study research to prove the association between of each characteristic, diagnostics and management to the outcome of PPHN.

Conclusion

The characteristics of PPHN in dr. Soetomo Hospital consist of, baby boy, with term infant, normal birth weight, perinatal history of asphyxia and MAS, with the complications of pneumonia, maternal history of eclampsia, and delivery procedures by C- section. PPHN could diagnosed with differences in pre- and post-ductal saturation, confirmed by echocardiography followed with the results moderate PPHN. The management of PPHN in dr. Soetomo Hospital was received oxygenation supplementation using mechanical ventilator and O_2 CPAP, with drug combination frequently used sildenafil with inotropic, sildenafil with illoprost and inotropic, and also sildenafil single administration. With the outcome of PPHN were in a cured condition.

Conflict of Interest : None declared.

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References

1. Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. Paediatr Respir Rev. 2015;16(3): 157–161.
2. Choudhary M, Meena M, Chhangani N, Sharma D, Choudhary J Choudhary S. To study prevalence of persistent pulmonary hypertension in newborn with meconium aspiration syndrome in western Rajasthan, India : a prospective observational study. J Matern-Fetal Neo M. 2015;1–4.
3. Coates EW, Klinepeter ME, O`Shea TM. Neonatal pulmonary hypertension treated with inhaled nitric oxide and high-frequency ventilation. J Perinatol. 2008;28: 675-679.
4. Hakeem A, Mohsen A, Amin AS. Risk factors and outcomes of persistent pulmonary hypertension of the newborn in neonatal intensive care unit of al-minya university hospital in Egypt. Journal of Clincal Neonatology. 2013; 2(2),p. 78–82.
5. Harish S, Kamalarathnam CN. Clinical profile of persistent pulmonary hypertension in new born : experience in an extramural institution', Int J Contemp Pediatr.2018;5(6): 2193–2198.
6. Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: Advances in diagnosis and treatment. Semin Fetal Neonatal Med J. 2015;20(4): 262–271.
7. Kahveci H, Yilmaz O, Avsar UZ, Ciftel M, Kilic O, Laloglu F, Ozturk K. Oral sildenafil and inhaled illoprost in the treatment of pulmonary hypertension of the newborn. Pediatr Pulm.2014;49(12): 1205–1213.
8. Konduri GG, Kim UO. Advances in the Diagnosis and Management of Persistent Pulmonary Hypertension of the Newborn. Pediatr Clin N Am.2009;56(3): 579–600.
9. Lakshminrusimha S, Keszler M. Persistent

Pulmonary Hypertension of the Newborn. NeoReviews.2015;16(12): e680–e692.

10. Lancelloti P, Cosyns B. The EACVI Echo Handbook. Oxford: University Press.2016.
11. Lazar DA, Cass DL, Olutoye OO *et al*. The use of ECMO for persistent pulmonary hypertension of the newborn : A decade of experience. J Surg Res.2012.177(2): 263-267
12. Mathew B, Lakshminrusimha S. Persistent Pulmonary Hypertension in the Newborn. Children.2017;4(63): 1–14.
13. Medical record dr. Soetomo Hospital, Surabaya; 2016.
14. Nair J, Lakshminrusimha S. Update On PPHN: Mechanisms And Treatment. Semin Perinato. 2014;38(2): 78–91.
15. Nakwan N. The Practical Challenges of Diagnosis and Treatment Options in Persistent Pulmonary Hypertension of the Newborn : A Developing Country's Perspective. Am J Perinat. 2018;35(14): 1366–1375.
16. Nakwan N, Chaiwiriyawong P. An international survey on persistent pulmonary hypertension of the newborn : A need for an evidence-based management. J Neonatal Perinatal Med.2016; 9: 243- 250.
17. Niermeyer S, Andrade MP, Vargas E, Moore LG. Neonatal oxygenation, pulmonary hypertension , and evolutionary adaptation to high altitude (2013 Grover Conference series). Pulm Circ.2015; 5(1): 48-62.
18. Roofthooft MTR, Elema A, Bergman KA, Berger RMF. Patient Characteristics in Persistent Pulmonary Hypertension of the Newborn. BMC Pulm Med. 2011; 1–8.
19. Ru-Jeng T, Wu TJ. Persistent pulmonary hypertension of the newborn. J Formos Med Assoc.2013;112: 177–184.
20. Samudro H, M. Djer M. Inhaled illoprost as part of combination therapy for persistent pulmonary hypertension of the newborn. Paediatrica Indonesiana. 2012;52(1): 57–60.
21. Sharma M, Mohan KR, Narayan S, Chauhan L. Persistent pulmonary hypertension of the newborn: A review. Med J Armed Forces India. 2011; 67(4): 348–353.
22. Storme L, Aubry E, Rakza T, *et al*. Pathophysiology of persistent pulmonary hypertension of the newborn: Impact of the perinatal environment. Arch Cardiovasc Dis Suppl. 2013;106(3): 169–177.
23. Walsh-sukys MC, Tyson JE dan Wright LL, *et al*. Persistent Pulmonary Hypertension of the Newborn in the Era Before Nitric Oxide : Practice Variation and Outcomes. Pediatrics. 2000;105(1): 14–20.
24. Wedgwood S, Lakshminrusimha S, Schumacker PT, Steinhorn RH. Hypoxia inducible factor signaling and experimental persistent pulmonary hypertension of the newborn. Front Pharmacol. 2015;6(47): 1–8.
25. Yaseen H, Darwich M, Hamdy H. Is sildenafil an effective therapy in the management of persistent pulmonary hypertension?. J Clin Neonatol. 2012;1(4): 171–5.
26. Yokoo N, Marumo C, Nishida Y, Iio J, Maeda S, Maihara T. Combination drug therapy for persistent pulmonary hypertension of the newborn. Health Edu Care. 2017;2(3): 1–2.
27. Luecke C and Mcpherson C. Treatment of Persistent Pulmonary Hypertension of the Newborn: Use of Pulmonary Vasodilators in Term Neonates. Neonatal Netw J Neonatal Nurs. 2017;36(3): 160–168.