ISSN 0974-3618 (Print)
0974-360X (Online)
www.rjptonline.org

RESEARCH ARTICLE

Pulmonary Hypertension in Neonates: Early identification and treatment

Agus Cahyono[1,2], Irwanto[3]*, Mahrus A Rahman[3], Widjiati Widjiati[4]
[1]Doctoral Program of Medical Science, Faculty of Medicine, Airlangga University, Surabaya, Indonesia.
[2]Department of Clinical Medicine, Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia.
[3]Department of Child Health, Faculty of Medicine, Airlangga University, Surabaya, Indonesia.
[4]Department of Veterinary Science, Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia.
*Corresponding Author E-mail: **irwanto@fk.unair.ac.id**

ABSTRACT:
Pulmonary hypertension (PH) in children often underrecognized due to lack of awareness to its risk factors and diagnosis tool. In neonate population, these factors become more challenging. When diagnosis is made early, the treatment can be commenced earlier for better prognosis. The objective of this article is to report explorational study of pulmonary hypertension in neonates. Medical records of neonatal intensive care unit (NICU) patients for a year was reviewed. All NICU patients underwent echocardiography screening of PH within 48 hour from admission. Patients with PH were included in the study and the data was described for sex, bodyweight, gestational status, associated conditions and outcome. In a year, 167 patients was recorded admitting NICU with male predominance (96 male versus 71 female). Twenty patients with PH were identified with male and female ratio 1:1, and low birthweight and preterm infants predominance, (12 out of 20). Furthermore asphyxia, respiratory distress syndrome, transient tachypneu of the newborn, necrotizing enterocolitis, and systemic inflammatory response syndrome were associated with PH. Five patients died during nursery. Three representative PH patients revealed dilation of right atrium and tricuspid regurgitation on echocardiography examination. These patients were put on continuous positive airway pressure machine and received oral sildenafil 2mg/kg bodyweight. One of them died due to multiple organ dysfunction syndrome. Early echocardiography revealed pulmonary hypertension in neonates.

KEYWORDS: Pulmonary, Hypertension, Neonate, Early, Echocardiography.

INTRODUCTION:
Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) ≥20mmHg at rest, measured by right heart catheherization.[1] Its prevalence is 15 until 50 cases/1million adults, meanwhile in children 2 until 16 cases/1million children. Eventhough its rarity, the prevalence in high risk group is higher.[2]

In neonates, PH can be present in preterm or term infants. Asphyxia, respiratory distress syndrome (RDS), bronchopulmonary dyplasia (BPD), and pneumonia are associated with PH in infants.[3] The diagnosis of PH in neonates is based on clinical findings such as hypoxemia, respiratory distress and proven by echocardiography.[4]

Prompt diagnosis is essential in management of PH in neonates. Echocardiography is a noninvasive modality in diagnosing PH and very valuable for neonates population. Its role in diagnosing PH is undoubted. Its findings of PH include right atrium (RA) dilation, inferior vena cava (IVC) dilation, right ventricle (RV) dilation, flattening of interventricular septum, persistent foramen ovale, increased velocity of tricuspid regurgitation (TR) jet, and decreased of Tricuspid annular plane systolic excursion (TAPSE).[5] Moreover, echocardiographic parameter such as pulmonary artery acceleration time to the right ventricular ejection time

Received on 02.08.2024 Revised on 26.12.2024
Accepted on 28.02.2025 Published on 05.09.2025
Available online from September 08, 2025
Research J. Pharmacy and Technology. 2025;18(9):4449-4454.
DOI: 10.52711/0974-360X.2025.00638

(PAAT:ET) is able to predict neonates with PH who will fall into extracorporeal membrane oxygenator (ECMO).[6]

Management of PH in neonates include supportive care, oxygenation, mechanical ventilation, surfactant, pulmonary vasodilator agents, vasoactive agents, and ECMO.[7] Since pathophysiology of PH is complex and every patients has its own unique of associated condition, every center has its own challenges to deal with PH in neonates. However, therapy principle is to bring pulmonary arterial (PA) pressure to normal pressure. Combining various modalities to normalize PA pressure is possible with cautious principle.[8] Here, we describe early identification of PH in neonatal patients admitting neonatal intensive care unit (NICU) in our hospital for a year. Three representative cases of PH in neonate patients with different associated condition and its treatment strategies were described in detail.

MATERIALS AND METHODS:

Materials:

Medical records of patients admitted neonatal intensive care unit (NICU) for a year were reviewed.

Method:

Medical records of NICU patients were reviewed for demographic data. All patients using ventilator or continuous posstive airway pressure (CPAP) were screened for PH by echocardiography within 48hour of NICU admission. Patients with PH were included in the study. The data was described on table depicting sex, birthweight, gestational status, associated condition, and outcome. Three representative PH patients were studied in detail. Informed consent was gained from parents of these patients.

Place and time of study:

The study was take place at Bhakti Dharma Husada Hospital, Surabaya, East Java, Indonesia from January 1st 2023 until December 31st 2023. Bhakti Dharma Husada Hospital is secondary referral hospital of West Surabaya, East Java, Indonesia.

RESULT:

Demographic data of NICU patients:

Within study period, 167 patients were admitted in NICU. Majority of patients was male (96 out of 167), with birthweight of more than 2500gram, with length of stay, with outcome, and with associated condition. Detail of data is depicted in table 1.

Table 1: Demographic data of NICU patients

Demographic	Number (%)
Sex	
Male	96 (57,5)
Female	71 (42,5)
Birthweight (gram)	
<1000	3 (1,8)
1000 - <1500	6 (3,6)
1500 - <2500	58 (34,7)
>2500	102 (61,1)
Length of stay (day)	
<7	42 (25,1)
7 - <14	67 (40,1)
14 - <21	29 (17,7)
>21	29 (17,7)
Associated conditions	
Respiratory distress syndrome (RDS)	56 (33,5)
Transient tachypneu of the newborn (TTN)	70 (41,9)
Meconeal aspiration syndrome (MAS)	3 (1,8)
Pneumonia	6 (3,6)
Multiple organ dysfunction syndrome	2 (1,2)
Outcome	
Discharged	156 (93,4)
Died	11 (6,6)

Twenty patients with PH is included in the study. No sex predominance in PH patients. However, most of patients were with low birthweight and born prematurely. Respiratory distress syndrome was the most associated conditions. Five patients died during nursery. Detail of data is described in table 2.

Table 2: Demographic data of pulmonary hypertension patients

Demographic	Number (%)
Sex	
Male	10 (50)
Female	10 (50)
Birthweight	
<1000	-
1000 - <1500	-
1500 - <2500	10 (50)
>2500	10 (50)
Gestational status	
Preterm infant	12 (60)
Term infant	8 (40)
Associated conditions	
RDS	10 (50)
TTN	3 (15)
Asphyxia	2 (10)
Pneumonia	1 (5)
MODS	2 (10)
Outcome	
Discharged	15 (75)
Died	5 (25)

Detail of 3 pulmonary hypertension cases:

Case 1

A 38 week of gestational age with birthweight of 3330 gram baby was born with respiratory distress. The baby was delivered by Cesarean section. The mother had history of fever 2 weeks before giving birth. Physical examination revealed baby with intercostae and subcostal retraction and increased respiratory frequency of 70x/minute, and peripheral oxygen saturation of 80%. Laboratory examination upon admission: hemoglobin (Hb) 11,7g/dL, white blood cells count (WBC) 23.2000/µL, platelets 197.000/µL, blood glucose 73 mg/dL, and C reactive protein (CRP) 0,08mg/dL. Babygram soon after birth revealed cardiomegaly and infiltrates on both lungs (Figure 1). The baby was put on

continuous positive airway pressure (CPAP) machine. He received Ampicillin sulbactam 2x200mg intravenously (iv), Dextrose 10% 240 ml/day, and Furosemide 2mg iv. He was diagnosed with transient tachypneu of the newborn (TTNB). A few hour later he suffered from gastric bleeding. Antibiotic was switched to meropenem 3x60mg and Amikacin 1x45 mg iv and fresh frozen plasma 30ml for 2 days was added to treatment. He was suspected sepsis and septic workup was held.

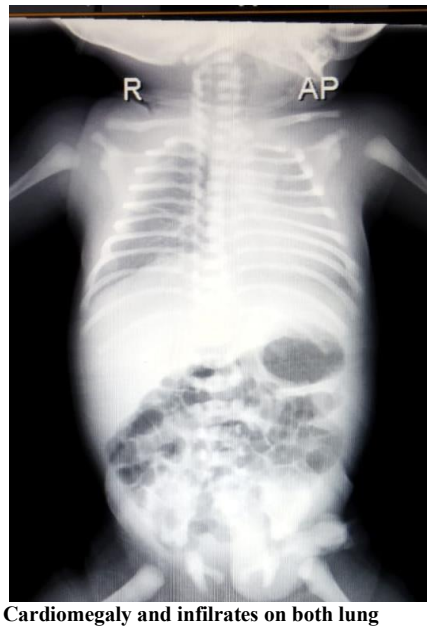

Figure 1: Cardiomegaly and infilrates on both lung

One day later, gastric bleeding was stopped and he received tropic feeding of breastmilk. The echocardiographic examination at one day of age revealed showed flat interventricular septum on systolic phase (Figure 2), mild dilatation of right atrium and ventricle, mild tricuspid regurgitation which consistent with pulmonary hypertension (PH), small secundum atrial septal defect (ASD), and small patent ductus arteriosus (PDA). He received Sildenafil 2mg per kilogram bodyweight a day, dobutamine 5µg/kg/minute, and Midazolam 0,05mg/kg/hour iv. Furosemide was withdrawn from treatment. The baby still showed intercostal retraction, tachypneu, and apneu occasionally. On the following day, Dopamin 3µg/kg/minute was added to treatment. No more apneu occurred after that. The feeding volume was increased as the baby tolerate.

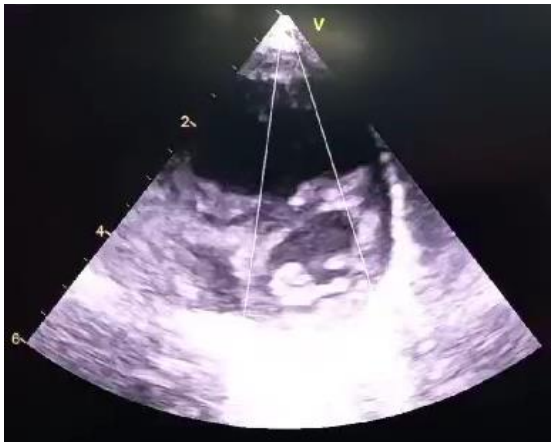

Figure 2: Flat interventricular septum on systolic phase

On 4th day of admission, the baby had hyperbilirubinemia with total bilirubin of 16,55mg/dL and indirect bilirubin of 15,77mg/dL. He was treated with fototherapy for 24hour. His clinical condition was improving afterward. The blood culture did not show positive for any bacteria and Amikasin was withdrawn after 8 days of treatment. However, Meropenem was continued until 15 days of treatment. On the 15th day of admission the inotropics were withdrawn form treatment. During hospitalization, parenteral nutrition was added to meet baby's callory need. Sildenafil eventually withdrawn after 18 days of treatment and one day later, the baby was discharged from the hospital.

Case 2

A 35 week of gestational age with birthweight of 2240 gram baby was born with respiratory distress. The baby was delivered by Cesarean section. Physical examination revealed baby with intercostae and subcostal retraction, increased respiratory frequency of 80x/minute, and peripheral oxygen saturation of 84%. Laboratory examination upon admission: Hb 14,9g/dL, WBC 26.750/µL, platelets 187.000/µL, blood glucose 50 mg/dL, and CRP 0,03mg/dL. Babygram soon after birth revealed cardiomegaly and mild granular opacification of lungs. She was diagnosed with respiratory distress syndrome (RDS). The baby was put on CPAP machine. She received Ampicillin sulbactam 2x150mg intravenously (iv) and Dextrose 10% 150 ml/day.

The echocardiographic examination at one day of age revealed mild-moderate tricuspid regurgitation (Figure 3), mild dilation of right atrium and ventricle, which consistent with PH and small PDA. The baby received sildenafil 2mg per kilogram bodyweight a day and furosemide 1mg iv. She was also with apneustic respiration therefore Aminophylline loading 10mg and continued with 2x5mg iv was add on treatment. Tropic feeding with breastmilk was given to her. Phenobarbital

loading 20mg continued with 2x5mg iv was added to treatment to sedate the baby.

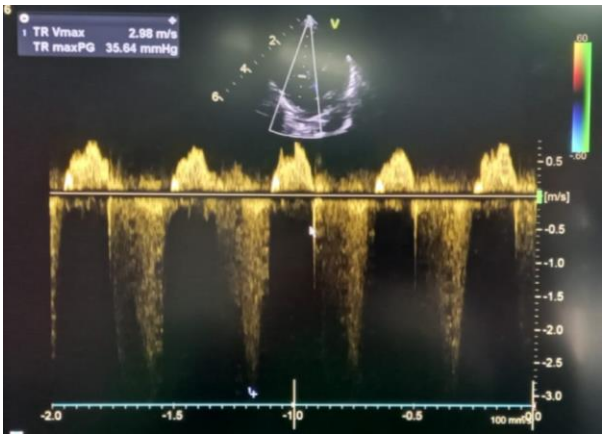

Figure 3: Tricuspid regurgitation

On the 3rd day of admission tachypneu still persisted, therefore Dobutamin 5 µg/kg/minute was added on treatment. On 5th day of admission, she still unable to tolerate tropic feeding and the abdomen distended therefore necrotizing enterocolitis (NEC) was suspected and furosemide was stopped and Dopamin 3µg/kg/minute was added on treatment. Dobutamin was stopped. Antibiotic was switched to Cefotaxim 2x100mg and Amikacin 1x20mg iv.

On the 7th day of admission apneustic respiration was not observed therefore Aminophylline was stopped. Dopamin was increased to 5µg/kg/minute. Sildenafil was stopped due to its adverse effect (gastrointestinal problem). The baby was able to tolerate tropic feeding and its volume was increased gradually afterward. During hospitalization, parenteral nutrition was added to meet baby's calories need.

Antibiotics were stopped at 10th day of treatment and CPAP was weaned on 17th day of treatment. She was able to tolerate full feeding on 19th day of treatment and on 24th day of treatment she was discharged from hospital.

Case 3

A 34 week of gestational age with birthweight of 2390 gram baby was born with respiratory distress. The baby was delivered by vaginal birth. His twin died in utero. Physical examination revealed baby with intercostae, subcostal retraction, anasarca, and hematuria. Laboratory examination upon admission: Hb 11,3g/dL, WBC 15.880/µL, platelets 126.000/µL, blood glucose 72mg/dL, CRP 0,47mg/dL, albumin 2,7g/dL, blood urea nitrogen (BUN) 13,9mg/dL, creatinine 1,48mg/dL, natrium 131mmol/L, potassium 4,7mmol/L, chloride 103mmol/L, and calcium 4,7mg/dL. Babygram soon after birth revealed cardiomegaly. He was diagnosed with RDS, acute kidney injury (AKI) and suspected sepsis. The baby was put on CPAP machine, received Cefotaxim 2x125mg iv, Dextrose 10% 160ml/day, albumin correction, calcium correction, fresh frozen plasma (FFP), furosemide 1x2,5mg iv and septic workup. Twelve hour after birth, he experienced seizure and treatment with Phenobarbital loading 25mg and continued with 2x6mg iv accompanied with Midazolam 0,05mg/kg/hour iv was commenced.

The echocardiographic examination at one day of age revealed mild dilation of right atrium and ventricle and mild-moderate tricuspid regurgitation which consistent with PH, secundum ASD, and small PDA with bidirectional shunt. Head ultrasonography revealed brain edema. Inotropic with Dopamin 5µg/kg/minute and Dobutamin 5µg/kg/minute were added on treatment.

On 4th day of admission he experienced apneustic respiration and anasarca became more prominent. Laboratory examination revealed albumin 2,8g/dL, natrium 102 mmol/L, potassium 5,7mmol/L, chloride 81 mmol/L, and calcium 8 mg/dL. On 6th day of admission AKI worsen, blood pressure dropped to 41/18mmHg and laboratory examination revealed BUN 47,9mg/dL, creatinine 3,58mg/dL, and blood culture did not show positive for any bacteria. Hydrocortisone 3x3mg iv and furosemide 1mg/kg/hour was added on treatment. Dopamin and Dobutamin were increased to 10 µg/kg/minute. Despite maximum treatment, he died on 17th day of admission.

DISCUSSION:

Patients admitting to NICU having greater risk of become PH. Our study proved 20 out of 167(12%) patients have PH. This number is much greater than in normal children which is 2-16 cases/million children.[2] We tabulate risk factors of PH in infants such as sex, gestational status, birthweight, and associated conditions related to PH. Our routine procedure is to examine every infants with CPAP or ventilator within first 48hour of NICU admission since it is important in recognizing PH as early as possible. Identification of risk factors of PH and early echocardiography screening is valuable in recognizing infants with PH.[4,6,9]

Pulmonary hypertension is condition when mPAP ≥20 mmHg by right heart catheterization. However, PH can be established by noninvasive echocardiography examination.[1] This condition in neonate also known as persistent pulmonary hypertension of the newborn (PPHN) can be experienced by preterm or term infant. In this population, it may cause significant morbidity or mortality.[3] Two of our case of neonatal pulmonary hypertension was improved with time, unfortunately 1

of cases died. The 2 survival cases required long nursery and high care at neonatal intensive care unit (NICU). Dynamic clinical condition that was faced by these babies such as apneustic respiration and NEC is very challenging and requires careful approach. Individual treatment adjustment based on patients need is necessary in our cases.

Diagnosing PH as early as possible is a challenge in neonate population. Clinical signs of PH oftenly similar to those other diseases such as cyanotic congenital heart disease and echocardiography is able to confirm the diagnosis.[4] Echocardiography is the most practical modality to asses PH. It can be done at first hour of life and able to uncover PH.[6] This practicality also benefit to hypertensive patients of adult population in recognizing diastolic dysfunction.[10] All of our cases were diagnosed as PH at first day of life due to accessibility of echocardiography. It has been become our NICU protocol to screen neonates as early as possible for PH.

Two dimensional (2D) echocardiography is able to evaluate the severity of PH. Dilation of right ventricular, right atrium, inferior vena cava and flattening of interventricular septum are the signs of PH. Doppler echocardiography may reveal tricuspid regurgitation (TR) jet and PDA and ASD shunt direction indicating severity of PH. The more severe of PH the more prominent of TR jet and of bidirectional shunt.[5] In our case, dilation of right ventricle and right atrium, TR jet were seen in all cases and flattening of interventricular septum was seen on 1st case. However, PDA with bidirectional shunt was seen in 3rd case.

Risk factors of PPHN include meconium aspiration, birth asphyxia, pneumonia, neonatal septicemia, congenital diaphragmatic hernia, infant delivered via Cesarean section, Asian maternal race.[11,12,13] Meanwhile, Cesarean section, birth asphyxia, and female sex are major risk factors associated with mortality in infants and RDS, birth asphyxia, and male sex are associated with increased mortality in preterm and postterm infants.[9] Urine serotonin, a promising marker in urine to determine degree of is understudy. This can be used as a tool to predict prognosis in infants with PH.[14] As in adults, Gremlin 1 is used to determine the severity of PH.[15] Two of our cases were delivered by Cesarean section and none of them died. In our cases, 2 of them were preterm infant and RDS, and one of them died. The death case was with complex problems mimicking septicemia. Administration of double dose of Betametasone to mother that is predicted of having preterm labor will reduce probability of RDS.[16]

Management of PPHN include general supportive care (maintain normal temperature, nutritional support, stress avoidance, maintain Hb>14g/dL, use of analgesia or sedative agents as needed), oxygenation, mechanical ventilation, surfactant, pulmonary vasodilator agents (inhaled nitric oxide, Sildenafil, Milrinone, Prostacyclin, Prostaglandin E1), supporting systemic blood pressure by vasoactive agents (epinephrine, nor-epinephrine, dobutamine, and low dose dopamine), and extracorporeal membrane oxygenation.[7] Sometimes patients with PPHN suffered from heart failure so that administration of intravenous furosemide will help.[17] Combining modalities to treat PH should be managed with caution.[8] We manage our cases with infant incubator to keep the babies warm, giving parenteral nutrition to meet calories need, oxygenation with CPAP machine with maximum franction of inspired oxygen of 60%, oral Sildenafil (in 2 cases), vasoactive agents, and furosemide. The babies were suggested having infection and treated with empiric antibiotics until proven otherwise. Sedative agents and anticonvulsant were used wisely considering individual needs.

CONCLUSIONS:

Pulmonary hypertension in neonate can be diagnosed early with echocardiography. Echocardiography findings in PH include dilation of right atrium, right ventricle, and main pulmonary artery, flattening interventricular septum during systolic, TR jet, and bidirection of PDA as the condition worsen. Treatment of PH is multimodality and holistic care should be taken in accordance with babies condition.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this case study.

ACKNOWLEDGMENTS:

The authors would like to thank NICU crew of Bhakti Dharma Husada Hospital for their gentle care to neonatal patients with pulmonary hypertension.

REFERENCES:

1. Humbert M. Kovacs G. Hoeper MM. Badagliacca R. Berger RMF. Brida M. Calrsen J. Coats AJS. Escribano-Subias P. Ferrari P. Ferreira DS. Ghofrani HA. Giannakoulas G. Kiely DG. Mayer E. Meszaros G. Nagavci B. Olsson KM. Pepke-Zaba J. Quint JK. Radegran G. Simonneau G. Sitbon O. Tonia T. Toshner M. Vachiery JL. Noordegraaf AV. Delcroix M. Rosenkranz S. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2023; 61: 2200879. doi: 10.1183/13993003.00879-2022
2. Hansmann G. Pulmonary hypertension in infants, children, and young adults. Journal of the American College of Cardiology. 2017; 69(20): 2551-2569. doi: 10.1016/j.jacc.2017.03.575.
3. Lakshminrusimha, S. Neonatal and postneonatal pulmonary hypertension. Children. 2021; 8(2): 131. doi: 10.3390/children8020131
4. Sharma V. Berkelhamer S. Laksminrusimha S. Persistent pulmonary hypertension of the newborn. Maternal Health Neonatology and Perinatology. 2015; 1: 14. doi: 10.1186/s40748-

015-0015-4
5. Jone PN. Ivy DD. Echocardiography in pediatric pulmonary hypertension. Frontiers in Pediatrics. 2014; 2: 124. doi: 10.3389/fped.2014.00124
6. Kipfmueller F. Akkas S. Pugnaloni F. Bo B. Lemloh L. Schroeder L. Gembruch U. Geipel A. Berg C. Heydweiller A. Mueller A. Echocardiographic assessment of pulmonary hypertension in neonates with congenital diaphragmatic hernia using pulmonary artery flow characteristics. Journal of Clinical Medicine. 2022; 11(11): 3038. doi: 10.3390/jcm11113038.
7. Singh Y. Lakshminrusimha S. Pathophysiology and Management of Persistent Pulmonary Hypertension of the Newborn. Clinics in Perinatology. 2021; 48(3): 595–618. doi: 10.1016/j.clp.2021.05.009
8. Gorenflo M. Ziesenitz VC. Treatment of pulmonary arterial hypertension in children. Cardiovascular Diagnosis and Therapy. 2021; 11(4): 1144-1159. doi: 10.21037/cdt-20-912
9. Razzaq A. Quddusi AI. Nizami N. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pakistan Journal of Medical Sciences. 2013; 29(5): 1099-1104. doi: 10.12669/pjms.295.3728
10. Thirumal BK. Nivetha R. Raja D. Radha S. Use of Doppler Echocardiography as a Prognostic Marker in Evaluating Hypertensive Patients with and without left Ventricular Hypertrophy – A Hospital Based Study in Vellore. Research Journal of Pharmacy and Technology. 2018; 11(9): 3983-3989. doi:10.5958/0974-360X.2018.00732.1
11. Delaney C. Cornfield DN. Risk factors for persistent pulmonary hypertension of the newborn. Pulmonary Circulation. 2012; 2(1): 15-20. doi: 10.4103/2045-8932.94818
12. Hernandez-Diaz S. Van Marter LJ. Werler MM. Louik C. Mitchell AA. Risk factors for persistent pulmonary hypertension of the newborn. Pediatrics. 2007; 120: e272-282. doi: 10.1542/peds.2006-3037
13. Mohsen AHA. 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 Clinical Neonatology. 2013; 2(2): 78-82. doi: 10.4103/2249-4847.116406.
14. Bilalova DF. Mindubayeva FA. Nigmatullina RR. Salikhova YY. Monocrotaline model of Pulmonary hypertension in immature rats from the perspective of Serotonergic regulation. Research Journal of Pharmacy and Technology. 2023; 16(8): 3915-3920. doi: 10.52711/0974-360X.2023.00644
15. Al-Najeem HT. Al-Dujaili ANG. Assessment of Gremlin-1 Level in Pulmonary arterial hypertension disease. Research Journal of Pharmacy and Technology. 2017; 10(11): 3803-3806. doi: 10.5958/0974-360X.2017.00690.4
16. Surendran HP. Louis DM. Naushad N. Tomy M. Sreelaksmi MS. Narmadha MP. Effect of Antenatal Betamethasone on Respiratory Distress Syndrome in Preterm Neonates. Research Journal of Pharmacy and Technology. 2022; 15(4): 1533-1536. doi: 10.52711/0974-360X.2022.00255
17. Shree J. Daniel CJ. Marsh C. Daniel JS. Lavanya S. A Study on Continuous Infusion versus Intermittent bolus dosing of Furosemide in Hospitalized Heart failure patients. Research Journal of Pharmacy and Technology. 2021; 14(5): 2814-2818. doi: 10.52711/0974-360X.2021.00496