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Research Paper

Investigation of the Frequency of Causes of Pulmonary Hypertension in Neonates

Mohammad Hosein Arjmandnia[1], Mohammad Aghaali[2], Mohammad Hosein Atarod[3], Farideh Alemi[3], Aboutaleb Mohammadi[1*], Maryam ShamekhiAmiri[4]

1. Department of Pediatrics, School of Medicine, Hazrat-e Fateme Masoume Hospital, Qom University of Medical Sciences, Qom, Iran.
2. Department of Family and Community Medicine, Neuroscience Research Center, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
3. Student Research Committee, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
4. Department of Surgery, School of Medicine, Qom University of Medical Sciences, Qom, Iran.

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ABSTRACT

Background and Aim: This study investigates the etiology of high blood pressure in the pulmonary vessels, its treatability, and the time required to normalize pulmonary arterial pressure. Determining treatability and selecting the appropriate treatment necessitates examining the causes of this condition.

Materials and Methods: This research was a descriptive cross-sectional study. The study population included all neonates admitted to the neonatal and neonatal intensive care unit (NICU) departments of Hazrat Masoumeh Hospital and Izadi Hospital, Qom City, Iran, between 2020 and 2021 who had pulmonary hypertension and had not previously undergone medical or surgical treatments. Sampling was performed using the census method. Variables, such as neonate's term or preterm, age, sex, pulmonary arterial pressure (measured by echocardiography), presence or absence of associated cardiac problems, and presence or absence of underlying diseases, were extracted from medical records.

Results: Among the risk factors and causes of pulmonary hypertension in hospitalized neonates, the frequencies of abnormalities were as follows: hernia and idiopathic cases, 4(0.9%); asphyxia, 8(1.9%); pneumothorax, 12(2.8%); congenital heart anomalies, 17(4%); sepsis, 38(8.8%); persistent ductus arteriosus, 53(12.3%); malignant cases, 78(18.1%); and respiratory distress syndrome, 196(45.6%).

Conclusion: The results indicated that cardiac disease is highly prevalent in neonates with pulmonary hypertension.

*** Corresponding Author:**
Aboutaleb Mohammadi, Assistant Professor.
Address: *Department of Pediatrics, School of Medicine, Hazrat-e Fateme Masoume Hospital, Qom University of Medical Sciences, Qom, Iran.*
E-mail: *dr.mohamady57@gmail.com*

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Introduction

The fetus had physiological pulmonary hypertension. Oxygenated blood enters the fetus via the placenta through the umbilical vein during the fetal period. Pulmonary vascular resistance is high during the fetal period due to anatomical, physical, biochemical, and hormonal factors. As a result, pulmonary artery pressure is also high [1]. Typically, pulmonary artery pressure falls immediately after birth and reaches adult levels, 25 mm Hg, by the age of two months [2]. Successful adaptation to extrauterine life requires a rapid increase in pulmonary blood flow at birth so that the lungs become a site for gas exchange [3]. The term "persistent pulmonary hypertension (PPHN)" has traditionally been used in term and near-term infants, but the diagnosis of this condition in preterm infants is increasing [4]. In PPHN, an increase in pulmonary blood pressure is often secondary to increased pulmonary vascular resistance. Pulmonary vascular incompatibility caused by lung parenchymal diseases, poor and incomplete development of pulmonary vessels, and reduced growth of pulmonary vessels are among the causes of increased pulmonary vascular resistance [5]. The prevalence of PPHN is about 0.4-6.8 per 1000 live births in the United States of America and 0.43-6 per 1000 live births in the United Kingdom, and the mortality rate due to this disease has been reported to be about 4% to 33% [6, 7]. The initial diagnosis of PPHN is usually based on clinical symptoms, such as cyanosis and persistent hypoxemia, and the diagnosis is confirmed by echocardiography [8]. Complications of this disease include right-to-left extrapulmonary shunting, resulting in the entry of hypoxic blood into the systemic bloodstream and the development of cyanosis. Transient tachypnea of the newborn (TTN) can also occur in PPHN [3]. Patients with this disease are at risk of long-term complications, such as impaired neurodevelopment and cognitive function and sensorineural hearing loss, after recovery and discharge from the neonatal intensive care unit (NICU). Therefore, they require multifaceted, long-term follow-up after discharge [9, 10]. Preterm infants with bronchopulmonary dysplasia may present with severe pulmonary hypertension after hospital [11]. In these cases, maladaptation of pulmonary blood flow is observed, and if not diagnosed and treated promptly, it may cause cor pulmonale. The typical clinical picture in patients with hypoxic respiratory heart failure is a difference of >5% in blood oxygen saturation before and after the duct. However, this difference will be less in cases with a right-to-left atrial shunt [12]. Clinical signs and symptoms suggestive of congenital heart defects include the presence of a heart murmur, decreased femoral pulse, abnormal shape or enlargement of the heart on chest radiography, differences in blood pressure between the upper and lower extremities, unresponsiveness to high oxygen concentrations, and unresponsiveness to inhaled nitric oxide or other vasodilators [13]. Delay in diagnosis and appropriate treatment of cyanotic heart disease worsens its prognosis. Therefore, a comprehensive echocardiographic evaluation is necessary to rule out structural abnormalities [14]. Some structural heart defects can mimic the clinical symptoms of PPHN, such as total anomalous pulmonary venous connection, transposition of the great arteries, pulmonary atresia with or without ventricular septal defect, severe tetralogy of Fallot, tricuspid valve atresia, and severe Ebstein's anomaly [15]. This study aims to investigate the causes of pulmonary hypertension in newborns hospitalized at Fatemeh Masoumeh Hospital and Izadi Hospital in Qom City, Iran.

Materials and Methods

This research was a descriptive cross-sectional study. The study population included neonates hospitalized in the intensive care units of Fatemeh Masoumeh Hospital and Izadi Hospital, for whom echocardiography was performed. Using the formula for determining the percentage in the population and based on previous studies [1], and considering the prevalence of causes equal to 0.5, precision 0.1, and alpha 0.05, a minimum sample size of 96 people was calculated. Sampling was performed using the census method. The inclusion criteria were all neonates hospitalized in the neonatal ward who underwent echocardiography from 2020 to 2021. The exclusion criteria included neonates who had undergone drug treatment with dobutamine, milrinone, or diaphragmatic hernia surgery. After obtaining the ethical code from the Ethics Committee of the Qom University of Medical Sciences, the researcher began sampling and reviewing the patients' records by referring to the records of newborns hospitalized in the neonatal ward and NICU of Fatemeh Masoumeh Hospital and Izadi Hospital. They selected neonates with PPHN who had not previously undergone drug or surgical treatment were selected. The variables studied, such as whether the newborn was term or preterm, age, sex, pulmonary artery blood pressure on echocardiography, the presence or absence of associated heart problems, and underlying diseases, were extracted from the records. Data were collected and entered into the SPSS software, version 26.

Results

The gender distribution of PPHN infants was 213 boys (49.5%) and 217 girls (50.5%). The mean gestational age of PPHN patients was 34.47±3.1 wk. Also, the mean parity and weight of PPHN patients were 1.71±0.7 and 2.05±0.65, respectively (Table 1). A total of 150 neonates (34.9%) were born at term, and the frequency of natural delivery was 221 neonates (51.4%) (Table 1).

Regarding risk factors and causes in PPHN infants, the results were as follows: Respiratory distress syndrome (RDS) (45.6%), malignant TTN (18.1%), persistent ductus arteriosus (PDA) (12.3), sepsis (8.8), congenital heart defect (CHD) (4), pneumothorax (2.8), asphyxia (1.9), idiopathic (0.9), hernia (0.9) (Table 2).

In addition, the frequency of neonatal cardiac anomalies was determined in this study, in which the frequency of diabetic-CAMP was 3(0.7%), total anomalous pulmonary venous return was 4(0.9%), and hypoplastic left heart syndrome was 4(0.9%). Also, the transposition of the great arteries was 6(1.4%). Patients were divided into three groups according to the severity of pulmonary hypertension: Mild, moderate, and severe; the frequency of each group is presented in Table 3. The severe type was observed in 33% of the patients and moderate in 30% of the patients.

Discussion

Pulmonary hypertension is a common complication of congenital cyanotic heart disease associated with a left-to-right shunt [15]. Congenital heart disease increases pulmonary vascular resistance and causes PPHN, followed by severe hypoxia [16]. The study by O'Connor et al. entitled “PPHN in premature infants,” which was written in 2017 as a review of related articles and writings, introduced the pathophysiology of pulmonary hypertension in premature infants, reduced lung growth and alveolarization, and concomitant reduced pulmonary vascular growth, which causes a decrease in the surface of pulmonary capillaries [17]. This study identified intrauterine growth restriction, infections and inflammation, and factors, such as preeclampsia, which cause a decrease in placental blood flow, as intrauterine factors effective in PPHN. Postnatal factors contributing to the development of pulmonary hypertension include poor growth, infection, use of mechanical ventilation and oxygen therapy, and altered hemodynamics, such as PDA. Inflammation, either from infection or other factors, has been identified as a risk factor for the progression of pulmonary hypertension in both animal models and humans [18]. Altered hemodynamics, such as systemic-to-pulmonary shunts, can promote pulmonary vascular remodeling and increase the risk of pulmonary hypertension [19]. Delaney and Cornfield conducted a study titled “risk factors for PPHN in neonates” and investigated factors that increase the risk of PPHN [20]. Cesarean section and non-labor delivery were identified as substantial independent risk factors for PPHN. In a case-control study in the United States military population, infants born by cesarean section were 5-fold more likely to develop PPHN than the controls. In this study, chorioamnionitis significantly increased the risk of PPHN by more than 3-fold. Maternal race (black, Asian) and high maternal body mass index were both associated with an increased risk of PPHN [5]. Prenatal exposure to certain medications increases the risk of PPHN. For example, intrauterine exposure to aspirin increases the risk of this disease by more than 4.9-fold and nonsteroidal anti-inflammatory drugs by more than 6-fold [13]. In a case-control study of 20 infants with PPHN, 14 had intrauterine exposure to selective serotonin reuptake inhibitors after 20 weeks of gestation [15]. However, our study did not measure these factors because they were retrospective, and maternal records were unavailable. In a study of 49 neonates with PPHN, the etiologies of these patients included maladaptation, maldevelopment, and pulmonary vascular underdevelopment, in order of highest to lowest [21]. Ershad et al. conducted a study to evaluate the causes of PPHN in Pakistani neonates. They

Table 1. Determination of the frequency of term and type of delivery of mothers with infants with PPHN

Variables		No. (%)
Term	Yes	150(37.9)
	No	280(65.1)
Delivery	Natural	221(51.4)
	Cesarean	209(48.6)

Table 2. Determining the frequency of causes and risk factors in PPHN infants

Variables		No. (%)
RDS	Yes	196(45.6)
	No	234(54.4)
Malignant TTN	Positive	78(18.1)
	Negative	352(81.9)
PDA	Positive	53(12.3)
	Negative	377(87.7)
SEPSIS	Positive	38(8.8)
	Negative	392(91.2)
CHD	Positive	17(4)
	Negative	413(96)
Pneumothorax	Positive	12(208)
	Negative	418(97.2)
Asphyxia	Positive	8(1.9)
	Negative	422(98.1)
Idiopathic	Positive	4(0.9)
	Negative	426(99.1)
Hernia	Positive	4(0.9)
	Negative	426(99.1)

Abbreviations: RDS: Respiratory distress syndrome; TTN: Transient tachypnea of the newborn; PDA: Persistent ductus arteriosus; CHD: Congenital heart defect.

showed that the patients were predominantly (66.3%) male, and 64% were full-term neonates (gestational age greater than 37 weeks). Common factors affecting PPHN included amniotic fluid aspiration (42.6%), asphyxia during delivery (39.3%), RDS (18.8%), and sepsis (27%) [22]. However, in our study, most neonates with PPHN were girls (50.5%), and 37.9% were term. In our study, the etiologies proposed for infants with PPHN included RDS (45.6%), malignant TTN (18.1%), PDA (12.3%), asphyxia (1.9%), and sepsis (8.8%). The results

Table 3. Frequency of severity of pulmonary hypertension in neonates with PPHN

Variables	No. (%)
Mild	159(37)
Moderate	130(30.2)
Severe	141(32.8)
Sum	430(100)

of our study indicate that the high prevalence of congenital heart defects and underlying factors, such as RDS and other causes, play a crucial role in the occurrence of this disease. These results also emphasize the need for early diagnosis and appropriate management of these infants.

Conclusion

Our study showed that congenital heart defects and underlying conditions, such as RDS, significantly influence pulmonary hypertension in hospitalized infants. These results emphasize the importance of early diagnosis and effective management of neonates to prevent long-term complications. Appropriate preventive and therapeutic measures are needed to reduce the prevalence of this disease in neonates and improve their clinical outcomes.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Qom University of Medical Sciences, Qom, Iran (Code: IR.MUQ.REC.1402.143).

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Authors' contributions

All authors equally contributed to this article.

Conflict of interest

The authors declared no conflict of interest.

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