



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Pulmonary air leak syndrome in term and late preterm neonates

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SUMMARY

Introduction/Objective Air leak syndrome is more frequent in neonatal period than at any other period of life. Its timely recognition and treatment is a medical emergency. We present results of a tertiary medical center in treatment of air leak syndrome in term and late preterm neonates.

Methods Neonates born between 34th 0/7 and 41st 6/7 gestational weeks (g.w.) who were treated for air leak syndrome in the Neonatal Intensive Care Unit of Mother and Child Health Care Institute, from 2005 to 2015 were included in the study. Anthropometric data, perinatal history, type of respiratory support prior to admission, chest radiography, type of pulmonary air leak syndrome and its management, underlying etiology, and final outcome were analyzed.

Results Eighty-seven neonates of an average gestational age 38.1 ± 1.9 g.w. were included in the study. The average birth weight was 3182.5 ± 55.5 g. Forty-seven (54%) were born by cesarean section and 40 (46%) were born by vaginal delivery. Prior to admission, 62.1% received supplemental oxygen, 4.6% were on nasal continuous positive airway pressure, and 21.8% were on conventional mechanical ventilation. Type of delivery did not significantly affect the appearance of pneumothorax, nor did the type of respiratory support received prior to admission ($p > 0.05$). The majority (93.1%) had pneumothorax, which was unilateral in 79%. The length of mechanical ventilation significantly affected the appearance of pneumothorax ($p = 0.015$). Low Apgar score in the first minute and the presence of pneumopericardium were significant factors predisposing for an unfavorable outcome.

Conclusion Improving mechanical ventilation strategies and decreasing the rate of perinatal asphyxia in term and late preterm neonates could diminish the incidence of pulmonary air leak syndrome in this age group.

Keywords: pneumothorax; newborn; respiratory insufficiency; mechanical ventilation

INTRODUCTION

Pulmonary air leak syndrome (PALS) comprises several different clinical conditions resulting from alveolar over distension and air leakage outside the lungs. It appears more frequently in neonatal period than in any other period of life [1]. This is due to some particularities of respiratory system and its physiology in neonates (poorly compliant lungs, absence of collateral ventilation, highly compliant chest wall, poor respiratory reserve etc.) [2]. Frequency of PALS is determined by gestational age, mode of delivery, underlying lung disease, therapeutic interventions, mechanical respiratory support [3–5].

The aim of the study was to present the frequency, pathogenesis and treatment of PALS in a group of term and late preterm neonates treated in a tertiary medical center. Risk factors, clinical course and outcome of neonates treated for PALS were also analyzed.

METHODS

We present a group of 87 neonates treated for PALS in Neonatal Intensive Care Unit (NICU) of Mother and Child Health Care Institute, Bel-

grade, from January 2005 to December 2015. All patients were born between 34th 0/7 to 41st 6/7 gestational weeks (g. w.). The following data were analyzed from medical records: gestational age, birth weight, mode of delivery, Apgar score, need for resuscitation and respiratory support after birth, type of PALS (pulmonary interstitial emphysema [PIE], pneumomediastinum, pneumothorax, pneumopericardium), clinical and radiographic findings, accompanying disorders, mechanical ventilation (mode, parameters and duration), treatment of PALS (spontaneous resolution or chest tube drainage) and final outcome. The diagnosis was based on a plain chest radiography. According to the common hospital practice, if thoracic drainage was indicated for treatment of pneumothorax, chest tube was inserted by a pediatric surgeon. Neonates who required mechanical ventilation were ventilated using conventional mechanical ventilation modes. The final outcome was considered favorable if the patient recovered and was discharged home without needing supplemental oxygen. A patient's death was considered an unfavorable outcome.

Categorical variables were identified and reported in percentage. Data were analyzed using SPSS (Kolmogorov–Smirnov χ^2 test for testing

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the normal distribution, Pearson's χ^2 test for testing the association of variables, Student's t-test for testing the difference between groups, univariate logistic regression). A p-value of < 0.05 was considered statistically significant.

The protocol and publication of the results were approved by the Ethics Committee of the Mother and Child Health Institute of Serbia (number 8/10).

RESULTS

During the observed 10-year period, out of 3,484 neonates hospitalized in the NICU, 91 were diagnosed with PALS, which makes 2.6% of all hospitalized neonates. Four neonates were born before 34 g. w. Since the study aimed to analyze term and late preterm neonates, these four patients were excluded and further analysis was based on 87 patients. Patients' demographic characteristics are presented in Table 1. The average gestational age was 38.1 ± 1.9 g. w. The average birth weight was $3,182.5 \pm 55.5$ g. In the late preterm subgroup, the average birth weight was $2,791 \pm 441.9$ g, while in the term subgroup it was $3,349 \pm 456$ g. There is a statistically significant difference in birth weight in these two subgroups of neonates ($t = 5.264$; $p < 0.001$).

Mean Apgar score was 7.1 ± 2.4 at the first minute and 7.9 ± 2.1 at the fifth minute. There is a statistically significant difference in Apgar score at the first and fifth minute ($t = 6.700$; $p < 0.001$). Apgar score significantly increased at fifth minute.

Forty-seven neonates (54.1%) were born by cesarean section, while 40 (45.9%) were born by vaginal delivery. There is no statistically significant difference in the mode of delivery ($p > 0.005$).

Type of respiratory support prior to admission to our hospital and type of PALS neonates developed are presented in Table 2.

On admission to the NICU, 77 (88.5%) neonates had pathological auscultatory findings on chest auscultation, 61 (70.1%) had signs of respiratory distress, and 53 (60.9%) had tachypnoea.

Chest radiography was a part of the initial workup and was described by an experienced radiologist as pathologic in 85.1% of neonates, while in 14.9% it was described as normal. Signs of PALS were present in 45 (51.7%) of patients. The distribution of PALS type on admission is presented in Table 2.

In 10 patients there were signs of air leakage in more than one thoracic cavity. The distribution of PALS type in those 10 patients is presented in Table 3. Out of five patients with pneumopericardium, one patient was symptom-free and had only a thin continuous band of lucency encircling the heart with no clinical significance, while four patients had pneumopericardium along with pneumothorax. Three out of five patients with pneumopericardium died.

In patients with pneumothorax, there was a complete pneumothorax in 54 (66.6%) and partial pneumothorax in 27 (33.3%) patients. Pneumothorax was unilateral in 64 patients, most commonly right-sided (60.9%). Patients'

Table 1. Patients' characteristics

Sex		
Male	54 (62.1%)	$p > 0.005$
Female	33 (37.9%)	
Gestational age at birth (g. w.)		
37 0/7–41 6/7	61 (70.1%)	$p < 0.005$
34 0/7–37 0/7	26 (29.9%)	
Mode of delivery		
Vaginal	40 (46%)	$p > 0.005$
Cesarean section	47 (54%)	
Average birth weight (g \pm SD)		
Term neonates	3,349 \pm 456	$p < 0.001$
Late preterm neonates	2,791 \pm 441.9	
Average Apgar score		
1st minute	7.1 \pm 2.4	$p < 0.001$
5th minute	7.9 \pm 2.1	
Perinatal asphyxia		
Present	57 (65.5%)	$p < 0.005$
Absent	30 (34.5%)	

g. w. – gestational weeks

Table 2. Distribution of patients in regard to type of respiratory support and type of pulmonary air leak syndrome

Type of respiratory support	
None	9 (10.3%)
Oxygen	54 (62.1%)
nCPAP	4 (4.6%)
MV	19 (21.8%)
Type of PALS	
PIE	3 (3.4%)
Pneumothorax	81 (93.1%)
Pneumomediastinum	10 (11.5%)
Pneumopericardium	5 (5.7%)

nCPAP – nasal continuous positive airway pressure; MV – mechanical ventilation; PALS – pulmonary air leak syndrome, PIE – pulmonary interstitial emphysema

Table 3. Distribution of pulmonary air leak syndrome type in patients with air leakage in several thoracic cavities

Types	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10
PIE	X	X							X	
PM			X	X	X	X			X	
PT	X	X	X	X	X	X	X	X	X	
PP						X	X	X	X	X
Final outcome	+	+	+	+	+	-	-	+	-	+

Pt – patient, PIE – pulmonary interstitial emphysema; PM – pneumomediastinum; PT – pneumothorax; PP – pneumopericardium; "+" – recovered and discharged home without supplemental oxygen; "-" – deceased

distribution in regard to pneumothorax type and its resolution is presented in Table 4.

Spontaneous resolution of pneumothorax was observed in 31% of patients, while 69% needed thoracic drainage. Median thoracic drainage length was four days (range 1–14 days). Median thoracic drainage in patients with unilateral pneumothorax was four days (1–14 days), while it was six days (1–13 days) in patient with bilateral pneumothorax. There is a statistically significant difference in the length of thoracic drainage in regard to the type of pneumothorax ($U = 195.5$; $p = 0.014$). After the insertion of thoracic chest

Table 4. Distribution of patients with pneumothorax in regard to its type and resolution

Pneumothorax			
Unilateral	64 (79%)	right-sided	39 (60.9%)
		left-sided	25 (30.1%)
Bilateral	17 (21%)		
Pneumothorax resolution			
Spontaneous	25 (30.9%)		
Thoracic drainage	56 (69.1%)		

Table 5. The underlying etiology in patients with pulmonary air leak syndrome

Underlying disease	n
Perinatal asphyxia	57
TTN	24
MAS	18
Sepsis	15
Pneumonia	10
RDS	9
Complex CHD	4
ICH gr III–IV	4
Multiple congenital anomalies	3
Fetal hydrops	1

TTN – transitional tachypnoea of newborn; MAS – meconium aspiration syndrome; RDS – respiratory distress syndrome; CHD – congenital heart defect; ICH – intracranial hemorrhage

tube, the chest radiography showed pulmonary expansion in 85% of patients, whereas 15% of patients needed thoracic tube revision.

During the ten year period of this study mechanical ventilation (MV) was used to treat 726 neonates. Signs of PALS appeared in 7.2% of all ventilated neonates. Of 87 patients analyzed in the study, radiographic signs of PALS were present in 40.2% of patients who previously did not receive MV. Most commonly used type of MV was synchronized intermittent mandatory ventilation, which was used in 81.5%, while intermittent positive pressure ventilation was used in 18.5% of patients. During the study period, high frequency ventilation was not available at our hospital. The average length of MV was 3.8 ± 7.2 days. In patients with spontaneous pneumothorax, the average length MV was 1.9 ± 2.9 days, whereas in those patients with an underlying pulmonary disease who developed pneumothorax in clinical course the average length of MV was 5.2 ± 9.1 days. There is a statistically significant difference in the length of MV in regard to an underlying condition (U-test 543,5; $p < 0.05$).

The underlying etiology of patients with PALS is presented in Table 5.

Most of our patients (78.2%) had favorable outcome, while 21.8% died. Univariate logistic regression model showed that the variable associated with greater risk for adverse outcome was lower Apgar score at the first minute ($p = 0.001$). The presence of pneumopericardium was at the limit of statistical significance ($p = 0.056$). In group of patients with an unfavorable outcome 63.1% neonates had severe perinatal asphyxia, 26.3% MAS and PPHN, 26.3% had sepsis and/or pneumonia. There were 21% neonates with intracranial hemorrhage (ICH), 21% with complex

congenital heart disease (CHD), 15% with congenital anomalies (e.g. Sy Pierre-Robin, polycystic renal dysplasia, tracheoesophageal fistula) and one patient with severe nonimmune fetal hydrops.

DISCUSSION

Pulmonary air leak syndrome appears more commonly in the first month of life than in any other period of life. The overall incidence is estimated to be about 1% of all neonates, although only 10% of patients are symptomatic [1, 3, 6]. It is more common in premature neonates, because of the increased incidence of respiratory distress syndrome (RDS) and need for MV. Pneumothorax is by far the most common type of PALS.

More than two-thirds of all premature labors occur between 34 0/7 and 36 6/7 g. w. [7]. This group of neonates, referred to as “late preterm”, stands somewhere between term, mature neonates and those extremely premature, whose prematurity carries well-known risks and long-time complications. This group of neonates experience significantly more morbidity than infants born at term [7, 8]. It is known that these patients have increased incidence of RDS, transitional tachypnoea of newborn (TTN), meconium aspiration syndrome (MAS) with/without persistent pulmonary hypertension of the newborn (PPHN), hypoglycemia, hyperbilirubinemia. When prolonged premature rupture of membranes occurs between 34th and 37th g. w., corticosteroids are not used for fetal lung maturation [7]. An updated Committee Opinion from the American College of Obstetricians and Gynecologists (ACOG), published in August 2017, expands antenatal corticosteroid recommendations to support betamethasone administration to women at high risk for late preterm birth (34th 0/7 – 36th 6/7 weeks) [9]. This is an important point since there is a significant incidence of RDS and TTN in neonates born at this gestational age. It will be of clinical interest to follow the incidence of respiratory problems in this group of neonates in the following years, as we expect it to decrease with the latest update of ACOG recommendations.

In the absence of spontaneous initiation of delivery, there is a lack of multiple hormonal changes, in the fetus and the mother, which induce lung maturation and fetal lung fluid clearance [7, 8, 10]. Thus neonatal adaptation to extrauterine life is more difficult, respiratory physiology is changed and the incidence of RDS and TTN is increased, along with its possible complications, such as PALS, respiratory insufficiency, and pneumonia [8]. It is well documented that delivery by cesarean section is associated with increased risk for pneumothorax, regardless gestational age, especially in the absence of spontaneous initiation of delivery [11]. The fact that there is no significant difference in the mode of delivery in our group of neonates and that there is as much as 54% neonates were delivered by cesarean section is probably due to the fact that all neonates treated in our hospital are transfers (there is no maternity within hospital), so the structure of patients is random.

Higher birth weight carries greater risk of spontaneous pneumothorax in term neonates [12]. This is probably because larger neonates are more commonly born by interventional delivery (vacuum or forceps) and interventions are used prior to complete clearance of lung fluid. During the first few breaths uneven distribution of transpulmonary pressure might precipitate pneumothorax. In our study group, we showed a statically significant difference in birth weight between term and late preterm subgroup of neonates.

It was noticed in the late 70s that primary spontaneous pneumothorax appears more often in term and postterm neonates, especially in the presence of perinatal asphyxia, difficult and prolonged vaginal delivery, resuscitation after birth, presence of blood in airways, meconium in the airways at first aspiration after birth [13]. Therapeutic measures such as bag and mask ventilation in delivery room and resuscitation are well known risk factors for PALS [14]. Most patients with primary spontaneous pneumothorax do not have symptoms or have only mild symptoms and require no treatment. In clinical practice, the majority of these neonates are managed by supplemental oxygen. Most of our patients (62.2%) received oxygenotherapy prior to admission to our hospital. The signs of respiratory distress in the maternity wards resulted in supplying oxygen as the first step of respiratory support in these neonates. This stands along with the fact that 70.1% of them had signs of increased work of breathing and 60.9% were tachypnoeic. A group of Canadian authors showed an interesting result that oxygenotherapy in term neonates with primary spontaneous pneumothorax does not shorten the time to its complete resolution [15].

Respiratory insufficiency occurs in late preterm and term neonates as one of the complications of perinatal asphyxia [8]. In the most severe cases of perinatal asphyxia chronic mechanical ventilation might be needed. In our group of patients, 65.5% were diagnosed with perinatal asphyxia.

Unfavorable outcome was observed in 21.8% of our patients, which can be explained by high percentage of patients with severe perinatal asphyxia and associated conditions that increase the risk of death. In the group of patients with unfavorable outcome, as many as 63% had severe perinatal asphyxia. This result stands in favor of the fact that a lot of effort must be put in preventing perinatal asphyxia in developing countries, as this is an important risk factor for both respiratory insufficiency, complications but also for and an unfavorable outcome.

Several pulmonary diseases such as RDS, TTN, MAS, pulmonary hypoplasia, pneumonia, increase the risk of PALS [16, 17]. Some of these were the most common underlying pulmonary diseases in our group of neonates, as they are frequent respiratory pathology in neonates born at term or late preterm gestation.

MV increases the risk for PALS. The use of surfactant in prevention and treatment of RDS along with modern concept of "gentle" MV significantly decrease the risk of PALS during MV of a neonate [18]. The wide use of nasal continuous positive airway pressure (nCPAP) and noninvasive ventilation diminishes number of neonates who require intubation and conventional MV, thus decreasing the risk of PALS. The use of high frequency ventilation in prevention and treatment of PALS is attracting more attention of neonatologists in the previous years [19]. Conventional MV was the only MV mode available in our hospital for most of the time during the ten-year period of this study, so we could not compare the incidence of PALS in regard to different respiratory support types.

Neonates with asymptomatic pneumothorax without underlying pulmonary disease do not require specific treatment. Needle aspiration with angiocatheter would be an acceptable, less invasive but efficient treatment modality, especially in a patient with mild symptoms, but there is, so far, only one small randomized trial to support its use in neonates [20]. In 69% of our patients, pneumothorax was treated by thoracic underwater drainage. The duration of thoracic drainage was statistically significantly longer in patients with pneumothorax due to an underlying disease, compared to those with spontaneous pneumothorax. Other invasive procedures commonly used in children and adults, such as video-assisted thoracoscopic surgery, are not used in neonates [21].

Statistical analysis distinguished two factors which are connected to an unfavorable outcome: low Apgar score in the first minute and the presence of pneumopericardium. We believe that the former result is of great clinical importance, as pneumopericardium is seen almost exclusively in patients on mechanical ventilation, so its appearance would demand increased vigilance of clinicians. We believe that our results are to be interpreted in the context of our study design which did not include the control group, so the true incidence of PALS in a larger sample of neonates could not be estimated.

CONCLUSION

Pulmonary air leak syndrome in neonates is a life-threatening condition and a medical emergency that requires prompt treatment. Wide use of surfactant in prevention and treatment of RDS, modern concept of noninvasive respiratory support and "gentle" mechanical ventilation lead to an important decrease in the incidence of PALS. A lot of effort should be put into perinatal asphyxia prevention, as it is an important risk factor for PALS in the group of term and late preterm neonates.

Conflict of interest: None declared.

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Плућни синдром цурења ваздуха код терминске и предтерминске новорођенчади

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САЖЕТАК

Увод/Циљ Плућни синдром цурења ваздуха је чешћи у неонаталном узрасту него у било ком периоду живота и његово благовремено препознавање и лечење спада у најхитнија стања у медицини. Приказујемо резултате терцијарног медицинског центра у лечењу плућног синдрома цурења ваздуха код терминске и предтерминске новорођенчади.

Методе Студијом су обухваћена сва новорођенчад рођена између 34. 0/7 и 41. 6/7 гестациске недеље која су током периода 2005–2015. лечена од плућног синдрома цурења ваздуха на Одељењу неонаталне интензивне неге Института за здравствену заштиту мајке и детета Србије. Анализиране су антропометријске карактеристике, присуство перинаталне асфиксије, примена и тип респираторне потпоре пре пријема, радиографија грудног коша, тип плућног синдрома цурења ваздуха, начин лечења, примарна етиологија болести и коначан исход.

Резултати Анализирано је 87 новорођенчади просечне гестациске старости $38,1 \pm 1,9$ гестациских недеља, просечне порођајне телесне масе $3182,5 \pm 55,5$ g. Њих 47 (54%) рођено је царским резом, док је 40 (46%) рођено природним

путем. Пре пријема, оксигенотерапија је примењивана код 62,1% новорођенчади, назални континуирани позитивни ваздушни притисак код 4,6%, а конвенционална механичка вентилација код 21,8% новорођенчади. Начин порођаја као ни врста респираторне потпоре примењиване пре пријема у неонаталну интензивну негу нису статистички значајно утицали на појаву знакова плућног синдрома цурења ваздуха ($p > 0,05$). Највећи број болесника имао је пнеумоторакс (93,1%), који је најчешће био једностран (79%). Дужина трајања механичке вентилације статистички је значајно утицала на појаву плућног синдрома цурења ваздуха ($p = 0,015$). Низак индекс бодовања по Апгаровој у првом минуту и присуство пнеумоперикарда су предиктивни фактори за неповољан коначни исход лечења.

Закључак Побољшање стратегије механичке вентилације и смањење учесталости перинаталне асфиксије код терминске и предтерминске новорођенчади могли би да допринесу смањењу учесталости плућног синдрома цурења ваздуха у овој групи болесника.

Кључне речи: пнеумоторакс; новорођенче; респираторна инсуфицијенција; механичка вентилација