Original Research Article

Pneumothorax in Preterm Neonates and Its Association with Intraventricular Hemorrhage

Abstract

Background: Haemorrhage into the periventricular subependymal germinal matrix with subsequent extension into the ventricles (intraventricular haemorrhage) is one of the major complications in premature infants which continues to pose challenges in neonatal intensive care units (NICUs) worldwide.The aim of this work was to test the hypothesis that a pneumothorax increases the risk of intraventricular hemorrhage in premature neonates.

Methods: This prospective study was carried out upon 40 premature neonates with pneumothorax. Patients were divided into two equal groups: group1: preterm neonates between 28-32 weeks gestation with pneumothorax and group2: preterm neonates between 32-36 weeks gestation with pneumothorax. All patients were subjected tolaboratory investigations [complete blood count (CBC), C- reactive protein (CRP), arterial blood gases (ABGs)], head ultrasonography, and plain x-ray.

Results: Birth weight, GA, and MABP were significantly lower in the intraventricular haemorrhage group compared to the normal group. There was a statistically significant difference in mortality between both studied groups. RD was significantly higher in the intraventricular haemorrhage group compared to the normal group.

Conclusions: Pneumothorax in preterm neonates was associated with an increase occurrence and severity of Intraventricular Haemorrhage. Our study shows that pneumothorax can induce IVH in neonates with a gestational age of less than 32 weeks and a birth weight of less than 1000 g. These severe degrees of intraventricular haemorrhage have been associated with early mortality.

Keywords: Pneumothorax, Preterm Neonates, Intraventricular Haemorrhage.

Introduction:

Pneumothorax occurs more frequently in the neonatal period than in any other period of life and is associated with increased mortality and morbidity. It is a relatively frequent critical situation in the Neonatal Intensive Care Unit (NICU). It begins with rupture of an over-distended alveoli and the air escapes along the perivascular connective tissue sheath into the pleural space, causing pneumothorax and less commonly pneumomediastinum, pneumopericardium, sub- cutaneous emphysema, and pneumoperitoneum, altogether known as air leak syndromes[1].

Symptomatic pneumothorax occurs in about 0.05% to 0.1% of all live births, and in very low birthweight neonates this rate can achieve 3.8% to 9% [2, 3]. Also, this rate can achieve up to 35% in those being ventilated for respiratory distress syndrome. Several risk factors for pneumothorax have been described and include immaturity, respiratory distress syndrome (RDS), invasive and non-invasive respiratory support, and chorioamnionitis[4].

Haemorrhage into the periventricular subependymal germinal matrix with subsequent extension into the ventricles (intraventricular haemorrhage) is one of the major complications in premature infants which continues to pose challenges in neonatal intensive care units (NICUs) worldwide[5].

There is a reduction in the incidence of IVH for preterm infants born at or above 26 weeks of gestation, but not for infants between gestational ages 22 weeks through 25 weeks[6].

Intraventricular haemorrhage (IVH) is one of the major causes of ~~the~~ cerebral palsy and mental retardation. The most important neurological manifestations of brain damage in preterm infants are cognitive and motor disabilities. A number of perinatal risk factors such as low birth weight, intrauterine infection, low Apgar score, acidosis, and sepsis have been associated with the pathogenesis of IVH[7].

Three factors appear to be central to the genesis of haemorrhage. The first relates to the inherent vulnerability of the germinal matrix, with immature vessels and poorly supportive gelatinous matrix[8].

The second relates to the concept of ~~a~~ pressure passive circulation often referred to as loss of autoregulation, and the third relates to perturbations in cerebral blood which are common in the sick premature infant. ~~Probability~~ The probability of clinical signs and symptoms tends to increase with the intensity of haemorrhage[9].

Numerous studies established an association between RDS and its complications, i.e., pneumothorax and IVH. The mechanisms linking the two conditions are mediated via systemic perturbations including fluctuations or rapid increases in blood pressure which are often precipitated in associations with complications such as a pneumothorax. Recent studies have shown the importance of fluctuating arterial blood pressure in the pathogenesis of IVH after pneumothorax. In fact, a striking association between pneumothorax and IVH has been documented and is perhaps related to increases in cerebral blood flow velocity and blood pressure occurring at the time of pneumothorax[10].

The aim of this work was to test the hypothesis that a pneumothorax increases the risk of intraventricular hemorrhage in premature neonates.

Patients and Methods:

This prospective study was carried out upon 40 premature neonates with pneumothoraxwithout previous history of IVH from 29weeks to36weeks old admitted to Neonatal Intensive Care Unit (NICU), Tanta University. The duration of research was conducted from July 2020 to March 2021.

Exclusion criteria were neonates with congenital malformations, syndromes and chromosomal abnormalities, blood diseases, infectious diseases (toxoplasmosis,rubella,

cytomegalovirus,herpes,syphilis, and human immunodeficiency infections), neonatal asphyxia or any birth trauma and IVH before developing pneumothorax.

Patients were divided into two equal groups: group1: preterm neonates between 28-32 weeks gestation with pneumothorax and group2: preterm neonates between 32-36 weeks gestation with pneumothorax.

~~An i~~Informed written consent was obtained from guardians of the patients. The study was done after approval from the Ethical Committee of the Faculty of Medicine, Tanta University.

All the studied patients in NICU were subjected to detailed history taking with special emphasis on demographic dataand cause of NICU admission, thorough clinical examination including vital signs with especial emphasis on anthropometric measurements, cardiac system, and respiratory systems. Routine laboratory investigations ~~including~~ includecomplete blood count,C-reactive protein,arterial blood gases, head ultrasonography, and plain x-ray. All the patients were monitored for noninvasive investigation, pulse oximetry to continuously monitor SaO2, and blood pressure.Samples were taken under complete aseptic conditions to avoid transmission of infection to the patient, trans-cranial probe for performing cranial sonar was inserted cautiously to avoid any risk of trauma, and under complete aseptic measures.

Statistical analysis

Data were fed to the computer and analysed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). ~~Significance~~ The significance of the obtained results was judged at the 5% level.

The used tests were: Chi-square test for categorical variables, to compare between different groups, Fisher's Exact or Monte Carlo correction for Chi-square when more than 20% of the cells have expected count less than 5, Student t-test for normally distributed quantitative variables, to compare between two studied groups, Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups, Paired t-test for normally distributed quantitative variables, to compare between two periods and Wilcoxon signed ranks test for abnormally distributed quantitative variables, to compare between two periods.A ~~two~~ two-tailed P value < 0.05 was considered significant.

Results:

Birth weight, GA were significantly higher in group B compared to group A.Cranial ultrasonography was statistically significantly different between both studied groups.Sex, length, HC, delivery, RR, HR, MABP, right pneumothorax, left pneumothorax and bilateral pneumothorax were insignificantly different between both studied groups. Table 1

Table 1: Comparison between the two studied groups according to demographic data, vital signs,cranial ultrasonography, and site of pneumothorax

		Group A (n = 20)	Group B (n = 20)	Test of sig.	*p*
Sex	**Male**	13(65.0%)	11(55.0%)	$\chi 2$=0.417	0.519
	Female	7(35.0%)	9(45.0%)		
Birth weight	**<1**	10(50.0%)	0(0.0%)	$\chi 2$=44.433*	<0.001*
	1 – <1.5	10(50.0%)	0(0.0%)		
	1.5 – 2.5	0(0.0%)	9(45.0%)		
	>2.5	0(0.0%)	11(55.0%)		
	Mean ± SD.	1.0 ± 0.12	2.58 ± 0.49	t=14.015*	<0.001*
GA		30.05 ± 1.50	35.30 ± 0.92	t=13.307*	<0.001*
Length		48.0 ± 2.36	48.80 ± 1.44	t=1.294	0.205
HC		33.80 ± 1.15	34.05 ± 0.94	t=0.751	0.457
Delivery	**Normal**	3(15.0%)	5(25.0%)	$\chi 2$=0.625	FEp=0.695
	CS	17(85.0%)	15(75.0%)		
RR		58.25 ± 6.13	53.50 ± 9.88	1.827	0.077
HR		147.50 ± 16.18	137.50 ± 17.73	1.863	0.070
MABP		46.75 ± 14.56	54.80 ± 11.44	1.944	0.059
Cranial	**Normal**	0(0.0%)	9(45.0%)	χ^2=11.613*	0.001*

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Ultrasonography	**IVH**	20(100.0%)	11(55.0%)		
	Grade I	2(10.0%)	9(81.8%)	χ^2=18.236	$^{MC}p<0.001^*$
	Grade II	3(15.0%)	2(18.2%)		
	Grade III	9(45.0%)	0(0.0%)		
	Grade IV	6(30.0%)	0(0.0%)		
	Mean ± SD.	2.39 ± 1.20	1.36 ± 0.67	U=50.50*	0.028*
Right pneumothorax		14(70.0%)	15(75.0%)	2.190	0.346
Left pneumothorax		1(5.0%)	3(15.0%)		
Bilateral pneumothorax		5(25.0%)	2(10.0%)		

Data are presented as mean ± SD or frequency (%). GA: Gestational age, HC: Head circumference, Cs: Cesarean section, RR: Respiratory rate, HR: Heart rate, MABP: Mean arterial pressure,IVH: Intraventricular hemorrhage

Mortality and RD were significantly higher in group A compared to group B. Apgar score, consanguity, pneumonia, neonatal sepsis, Hf and P-cmv were insignificantly different between both studied groups. Table 2~~Table 2~~

Table 2: Comparison between the two studied groups according to Apgar score, mortality, consanguity, diagnosis, and ventilation techniques

	Group A (n= 20)	**Group B(n= 20)**	t	*p*
Apgar score at 1 min	5.85 ± 0.88	6.05 ± 1.10	0.637	0.528
Apgar score at 5 min	6.35 ± 1.18	7.0 ± 1.26	1.685	0.100
Died	15(75.0%)	7(35.0%)	6.465*	0.011*
Positive	3(15.0%)	1(5.0%)	1.111	0.605
RD	19(95.0%)	13(65.0%)	5.625*	0.044*
Pneumonia	1(5.0%)	4(20.0%)	2.057	0.342
Neonatal sepsis	0(0.0%)	3(15.0%)	3.243	0.231
Hf	7(35.0%)	3(15.0%)	2.133	0.144
P-cmv	13(65.0%)	17(85.0%)		

Data are presented as mean ± SD. RD: Respiratory distress, Hf: High Frequency,P-cmv: pressure-controlled mode of ventilation.

Birth weight, GA, and MABP were significantly lower in the intraventricular haemorrhage group compared to the normal group.There was a statistically significant difference in mortality between both studied groups.RD was significantly higher in the intraventricular haemorrhage group compared to the normal group. Table 3

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Table 3: Relation between cranial ultrasonography and demographic data, mortality, consanguity, diagnosis, vital signs and ventilationtechniquesin total sample (n = 40)

		Normal (n = 9)	IVH (n = 31)		
Sex	**Male**	7(77.8%)	17(54.8%)	χ^2=1.529	^{FE}p=0.272
	Female	2(22.2%)	14(45.2%)		
Birth weight	**<1**	0(0.0%)	10(33.3%)	χ^2= 11.935*	^{MC}p=0.003*
	1 – <1.5	0(0.0%)	10(33.3%)		
	1.5 – 2.5	3(33.3%)	6(19.4%)		
	>2.5	6(66.7%)	5(16.1%)		
	Mean ± SD.	2.70 ± 0.43	1.53 ± 0.78	t=5.819*	<0.001*
GA		35.22 ± 0.83	31.94 ± 2.91	t=5.554*	<0.001*
Length		48.56 ± 1.88	48.35 ± 2.03	t=0.266	0.792
HC		34.33 ± 0.50	33.81 ± 1.14	t=1.342	0.187
Delivery	**Normal**	4(44.4%)	4(12.9%)	χ^2= 4.337	^{FE}p= 0.059
	CS	5(55.6%)	27(87.1%)		
Died		0(0.0%)	22(71.0%)	14.194*	<0.001*
Positive		1(11.1%)	3(9.7%)	0.016	1.000
RD		4(44.4%)	28(90.3%)	9.176*	0.008*
Pneumonia		3(33.3%)	2(6.5%)	4.608	0.065
Neonatal sepsis		2(22.2%)	1(3.2%)	3.628	0.121
RR		51.67 ± 9.01	57.10 ± 8.04	1.738	0.090
HR		140.0 ± 15.0	143.23 ± 18.33	0.482	0.633
MABP		59.78 ± 8.93	48.16 ± 13.64	2.398*	0.022*
Hf		2(22.2%)	8(25.8%)	0.048	1.000
P-cmv		7(77.8%)	23(74.2%)		

Data are presented as mean ± SD or frequency (%).IVH: Intraventricular hemorrhage,GA: Gestational age, HC: Head circumference, Cs: Cesarean section, RD: Respiratory distress, RR: Respiratory rate, HR: Heart rate, MABP: Mean arterial pressure,Hf: High Frequency,P-cmv: pressure-controlled mode of ventilation.

Discussion

Pneumothorax occurs more frequently in the neonatal period than in any other period of life and is associated with increased mortality and morbidity. It begins with the rupture of ~~an~~ over-distended alveoli. The air escapes along the perivascular connective tissue sheath into the pleural space, causing pneumothorax and less commonly pneumomediastinum, pneumopericardium, subcutaneous emphysema, and pneumoperitoneum, altogether known as air leak syndromes[11].

As regards cranial sonar in group A, there is 20 (100%) had IVH In group B, there is 11 (55%) had IVH, there is a statistically significant difference between both studied groups as

regards cranial sonar, there is a statistically significant difference between both studied groups as regards grade of IVH.

Low birth weight was a risk factor ~~of~~ forIVH development as Our study shows~~that~~ theprevalence of IVH in group A, with a Mean birth weight with.0 ± 0.12 (Max 1 - <1.5 kg, Min < 1 Kg), there is 20 (100%) had IVH In group B with Mean birth weight with 2.58 ± 0.49 (Max >2.5 kg, Min 1.5 – 2.5 Kg)., there is 11 (55%) had IVH.

These~~s~~ result agree with the study of Pishvaet al.,[12] that show, Prevalence of IVH in preterm infants was 30%. 26 male neonates and 18 female ones developed IVH ~~it~~ whichmeans that the sex of infants did not affect IVH. Among neonates with IVH, 31 neonates (70%) had a birth weight of less than 1500 g, so low birth weight was a risk factor ~~of~~ forIVH development.

A close association between pneumothorax and the occurrence and extension of intraventricular haemorrhage has been reported previously by Dykes et al., [13]who found that if a premature infant had an alveolar rupture, the risk of intraventricular haemorrhage was increased 2-5-fold compared with similar infants without alveolar rupture.

In study in our hands we found that there is significant difference between both studied groups as regards Diagnosis (Respiratory Distress) and Mortality.

~~The~~ In the study of Pishvaet al.,[12] 91 neonates (60%) had respiratory distress syndrome (RDS), 7 neonates had pneumonia, 44 neonates (30%) developed IVH and 15 neonates (10%) had a pneumothorax.

Abdellatif et al., [14]found that the mortality was significantly higher with lower birth weights and gestational ages.

In our study we illustrated that according to Cranial Ultrasonography, there was no statistically significant difference between normal and IVH groups in sex distribution within the two groups, mean length or in the mean head circumference, or type of delivery.

There was a significant difference between normal and IVH groups as regards Birth weight and GA.

Pishva et al., [12]found that among neonates with IVH, 31 neonates (70%) had a birth weight of less than 1500 g, so low birth weight was a risk factor ~~of~~ forIVH development.

Linder et al., [15]found that there was an insignificant difference between the occurrence of IVH and demographic data (GA and birth weight).

The difference between the results could be explained due to the different sample sizes in each study and different criteria of the neonates according to the country.

In our study ~~in our hands~~, we demonstrated that according to cranial sonar, there was a significant difference between normal and IVH groups as regards Mortality.

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As regards respiratory distress; in this study, we found that according to cranial sonar, there was a significant difference between normal and IVH groups as regards RD p value equal 0.008

We found that among 31 neonates with IVH, 28 neonates had respiratory distress syndrome (RDS), ~~it~~ whichmeans that RDS was a risk factor ~~of~~ forIVH development in preterm infant with pneumothorax.

Pishva et al., [12]found that among neonates with IVH, 32 neonates had respiratory distress syndrome (RDS), ~~it~~ whichmeans that RDS was a risk factor ~~of~~ forIVH development in preterm infant.

Lee et al.,[16] found that the respiratory distress syndrome (RDS) was significantly higher in the IVH group than in the Normal group.

As regards main arterial blood pressure; In this study we illustrated that according to cranial sonar, there was significant difference between normal and IVH groups as regards main arterial blood pressure our study shows mean ± SD (59.78 (± 8.93SD) in normal group and

48.16 (±13.64SD) in IVH group There was a statistically significant difference between normal and IVH groups as regards main arterial blood pressure.

In the study of Mehrabani et al.,[17] regarding ~~to~~ grade of IVH show thirty-two infants, 89% of those in the hypotensive group, had grade 3 or 4 haemorrhages. The increased incidence of grade 3 or 4 intraventricular haemorrhage in this group of infants with pneumothorax and hypotension is highly significant compared with the group whose blood pressure remained normal (3 of 31, 10%). The relative risk of grade 3 or 4 intraventricular haemorrhage was 9-8 for infants who became hypotensive compared with those whose blood pressure remained normal.They show the incidence of intraventricular haemorrhage only one infant (3%) in the hypotensive group had a normal cranial ultrasound scan compared with 24 infants (77%) in the group with normal blood pressure.

We believe that cerebral hypoperfusion or ischemia precedes the development of severe intraventricular haemorrhage. It is possible that the cerebral hypoperfusion that accompanies the systemic hypotension causes infarction of both the periventricular white matter and the germinal matrix layer; when the blood pressure and cerebral blood flow are raised to normal values, the germinal matrix capillaries rupture, and germinal matrix or intraventricular haemorrhage develop.

We put forward the hypothesis that neonates with birth weight less than 1000 g lack cerebral autoregulation so that hypotension ~~induces~~ induced by pneumothorax can cause IVH. And after gestational age 28-week cerebral autoregulation development help to prevent IVH induced by hypotension ~~resulted~~ resulting from pneumothorax.

Unfortunately, our study has some limitations including that it is a single center study, the relatively small sample size, limited time of the study, and limited ~~follow~~ follow-up duration. Therefore, we could only assess short-term associations ofpneumothorax with intraventricular haemorrhage in preterm neonates.

Conclusions:

Pneumothorax in preterm neonates was associated with an increase occurrence and severity of intraventricular haemorrhage. Our study shows that pneumothorax can induce IVH in neonates with gestational age of less than 32 weeks and a birth weight of less than 1000 g. These severe degrees of intraventricular haemorrhage have been associated with early mortality.

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