

## Intraventricular Hemorrhage in Premature Infants and Its Association with Pneumothorax

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**Abstract-** Intraventricular hemorrhage (IVH) is one of the major causes of the cerebral palsy and mental retardation. Prevention and early management of these neurologic developmental problems will require determining the perinatal risk factors associated with this clinical entity. Pneumothorax increase the risk of IVH, and cause of pneumothorax has an important effect in severity of IVH. This is a prospective cross sectional study in 2010. This study includes 150 preterm neonates. Cranial ultrasound was performed in all neonates in age 3, 7, 30, 60, just after pneumothorax and every 2 week until chest tube discontinuation. Then prevalence of IVH and pneumothorax was calculated in preterm infant and severity of IVH was investigated before and after development of pneumothorax, and this comparison was divided by different causes of pneumothorax with SPSS version 11.5. Prevalence of IVH and pneumothorax in preterm infants were 30% and 10% respectively. Pneumothorax was not a risk factor of IVH ( $P>0.05$ ), but prevalence of pneumothorax caused by RDS was a risk factor of development of IVH ( $P=0.01$ ). Also pneumothorax in patients with birth weight less than 1000 g and gestational age less than 28 week was a risk factor of IVH pneumothorax ( $P=0.008$ ,  $P=0.01$  respectively). Our study discusses the differences in previous studies about association of pneumothorax and IVH. Also we suggest the hypothesis that lack of cerebral autoregulation in neonates with gestational age less than 28 week can cause IVH development after hypotension induces by pneumothorax.

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### Introduction

During the last few decades, the survival of preterm infants has increased dramatically (1,2) and approximately 85% of these infants survive (3). This improvement is mainly due to advances in perinatal medicine and neonatal intensive care. Nevertheless, the incidence of neurological impairment remains high among preterm survivors. Intraventricular hemorrhage (IVH) is one of the major causes of the cerebral palsy and mental retardation. The incidence ranges from 15% to 40%, depending on the center in spite of the many efforts to reduce the incidence (4,5). The most important neurological manifestations of brain damage in preterm infants are cognitive and motor disabilities. Prevention and early management of these neurologic developmental problems will require determining the

perinatal risk factors associated with this clinical entity. A number of perinatal risk factors such as low birth weight, intrauterine infection, vaginal delivery, low Apgar score, acidosis and sepsis have been proposed as associated with the pathogenesis of IVH (6-8).

Pulmonary air leak (pneumothorax) is another common complication in very low birth weight (VLBW) infants, accruing in up to 35% of those being ventilated for respiratory distress syndrome (9,10). Several reports have indicated that pneumothorax is often associated with, or followed by, intraventricular hemorrhage (11-15). But other studies have not reported an increased risk of IVH (16,17). None of these studies however commented on the severity of IVH caused by pneumothorax, whether the cause of pneumothorax had effect on severity of IVH.

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In this study we tested the hypothesis that a pneumothorax increase the risk of IVH, and cause of pneumothorax has an important effect in severity of IVH.

### Patients and Methods

This is a prospective cross sectional study. This study includes 150 preterm neonates (GA<37 week) referred to Hospitals affiliated to Shiraz University of Medical Science, during March 2010 to September 2010. Cranial ultrasound, according to the clinical protocol of the neonate intensive care unit (NICU), was performed in days 3 and 7 of NICU admission in all neonates and also in the age of 30 days and 60 days as well. Also brain sonography was performed in the patient after developing pneumothorax, and then rechecked twice a week until discontinuation of chest tube insertion. The severity of intraventricular hemorrhage was graded according to Papile *et al.* (11). Papile *et al.* categorized IVH in to 4 grades (11). Grade 1: Hemorrhage limited to the germinal matrix; Grade 2: Hemorrhage with extension to the ventricles, without dilatation of the ventricles; Grade 3: Hemorrhage with extension to the ventricles, with dilatation of the ventricles; Grade 4: Hemorrhage with parenchymal extension. Then prevalence of IVH and pneumothorax was calculated in preterm infant and severity of IVH was investigated before and after development of pneumothorax, and this comparison was divided by different causes of pneumothorax.

### Statistical analysis

Statistical analysis was performed with SPSS version 11.5. Chi-square and Fisher’s exact test were used to compare categorical variables. All variables that achieved significance ( $P<0.05$ ) on univariate analysis were identified and entered into a stepwise logistic regression analysis.

### Ethics

Our study was according to Helsinki ethics protocol and approved by local ethics committee of Shiraz University of Medical Science, ethics department. All of the parents involved in our study sign the informed

consent after describing the aim and method of the research.

### Results

150 preterm neonates were included in this study. 78 neonate were male (52%) and 72 neonates were female (48%). Mean gestational age of neonates at birth was 31 week (Max: 36 wk, Min: 24 wk). Mean birth weight of neonates was 1411 g (Max: 2660 g, Min: 610 g). 91 neonates (60%) had respiratory distress syndrome (RDS), 7 neonates had pneumonia, 44 neonates (30%) developed IVH and 15 neonates (10%) had pneumothorax (Table 1).

Prevalence of IVH in preterm infants was 30%. 26 male neonates and 18 female ones developed IVH it means that sex of infants did not affect IVH ( $P>0.05$ ). Among neonates with IVH, 31 neonates (70%) had birth weight less than 1500 g, so low birth weight was a risk factor of IVH development ( $P=0.002$ ). Among neonates with IVH, 32 neonates had respiratory distress syndrome (RDS), it means that RDS was a risk factor of IVH development in preterm infant ( $P=0.001$ ). Six neonate with pneumothorax had IVH, so pneumothorax was not a risk factor of IVH ( $P>0.05$ ), but if the pneumothorax caused by RDS, it rises the risk of IVH ( $P=0.01$ ). Also pneumothorax in patients with birth weight less than 1000g and gestational age less than 28 week was a risk factor of IVH progression ( $P=0.008$ ,  $P=0.01$  respectively), (Table 2).

Among 44 preterm neonates with IVH 36 of them had IVH grade 1 or 2, and 8 neonates had IVH grade 3 or 4 (table3). Half of severe IVH (grade 3 or 4) developed after pneumothorax and all the severe IVH developed in patients with RDS. Also our study showed severity of IVH in neonates with birth weight of less than 1000 g and gestational age less than 28 week was aggravated after development of pneumothorax ( $P=0.02$ ). But after pneumothorax happening in patients with birth weight of more than 1000 g and gestational age more than 28 wk, there is no IVH development or maximum a low grade IVH developed (grade 1 or 2). Aggravation of IVH grading after pneumothorax, also was seen in patients with RDS ( $P<0.05$ ).

**Table 1.** Distribution of preterm neonatal morbidity in our patients.

Sex	RDS	Pneumonia	IVH	Pneumothorax
Male	51	6	26	9
Female	40	1	18	6
Total	91	7	44	15

**Table 2.** Association of neonatal factors with IVH development.

Neonatal factors	Number (%) in IVH neonates	P-value of association of factors & IVH
Low Birth weight	31(70)	0.002
Sex	F:18(45), M:26(55)	>0.05
RDS	32(73)	0.001
Pneumothorax	6(15)	>0.05

**Table 3.** IVH severity grade in our patients according to Papile *et al.* (11) categorization.

IVH Grade	Number
1	21
2	15
3	5
4	3
total	44

## Discussion

Intraventricular hemorrhage occurs in about 35% of premature neonates weighing less than 1500 g at birth and is an important cause of mortality and morbidity (12). Intraventricular hemorrhage that originates in the capillary network of the germinal layer (a highly vascular and poorly supported layer). The intraventricular hemorrhage pathogenesis is so complex, but its occurrence is highest in VLBW infants with respiratory distress syndrome (11). A close association between pneumothorax and the occurrence and extension of intraventricular hemorrhage has been reported previously by Dykes *et al.* who found that if a premature infant had an alveolar rupture, the risk of intraventricular hemorrhage was increased 2.5 fold compared with similar infants without alveolar rupture (13). Of all the risk factors studied, they showed that the pneumothorax had the strongest association with the development of intraventricular hemorrhage. Lipscomb *et al.* (12) and Hill *et al.* (14) also reported a close relationship between intraventricular hemorrhage and pneumothorax. Cooke (15), and Van De Bor *et al.* (16) however did not show a high incidence of intraventricular hemorrhage in premature infants with pneumothorax. The difference among these previous studies might be resulted due to differences in the cause of the pneumothorax and in the patients gathered in those researches. Pneumothorax in an infant can be full asymptomatic or associated with severe circulatory disturbances including hypotension and hypoperfusion. When severe pneumothorax leads to inadequate cardiac filling and systemic hypotension (air block syndrome

cerebral ischemia may be induced, with the arterial watershed zones in the periventricular regions of the brain being particularly prone (11). Sarkar *et al.* showed that pneumothorax alter the risk of severe IVH (19).

Our study showed that prevalence of IVH in preterm (GA <37 wk) infant is 30%. Low birth weight, RDS and prematurity increase the risk of IVH. Pneumothorax in overall preterm infant is not a risk factor of IVH, but pneumothorax can induce IVH in neonates with gestational age less than 28 week and birth weight less than 1000 g. It can discuss the difference between the previous studies about association of pneumothorax and IVH. Difference in previous studies is due to difference in patients' birth weight and gestational age sampled for their research. Also our study showed that all pneumothorax caused by RDS can aggravate or induce IVH, so cause of pneumothorax can influence happening or aggravating IVH. In this research we saw that half of severe IVH (grade 3 or 4) developed after pneumothorax. Also we saw that seventy of IVH in neonates with birth weight of less than 1000 g and gestational age less than 28 week was aggravated after development of pneumothorax. But after pneumothorax happening in patients with birth weight of more than 1000 g and gestational age more than 28 wk, there is no IVH development or maximum a low grade IVH developed.

We believe that cerebral hypoperfusion or ischemia precedes development of severe intraventricular hemorrhage (18). 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 hemorrhage develop.

We put forward the hypothesis that neonates with gestational age less than 28 week or birth weight less than 1000 g lack cerebral autoregulation so that hypotension induced by pneumothorax can cause IVH. And after gestational age 28 week cerebral

autoregulation development help to prevent IVH induced by hypotension resulted from pneumothorax. More studies should be done to prove this hypothesis. In conclusion, our study shows that pneumothorax is not a risk factor of IVH in all preterm infant, but pneumothorax can induce or aggravate IVH in neonates with gestational age less than 28 week and birth weight less than 1000 g. Our study discusses the differences in previous studies about association of pneumothorax and IVH. We saw that cause of pneumothorax may important in IVH induction or aggravation. Also we suggest the hypothesis that lack of cerebral autoregulation in neonates with gestational age less than 28 week can cause IVH development after hypotension induces by pneumothorax.

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