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Continuous Positive Airway Pressure andPneumothorax in Neonates: two Large Baghdad Teaching Hospitals Report

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Abstract
Background: *Continuous positive airway pressure (CPAP) is a noninvasive form of respiratory assistance to support spontaneously breathing infants with lung disease. The risk for pneumothorax is higher in infants with respiratory distress syndrome, meconium aspiration syndrome, and pulmonary hypoplasia and in infants who need resuscitation at birth. CPAP further increases the incidence of pneumothorax.*
Objectives: *To study maternal and neonatal risk factors that was associated with pneumothorax after using CPAP.*
Patients and Methods: *This descriptive Prospective study started from March 15, 2014 to March 15, 2015. It includes 1000 registered neonates: 628 (62.8%) neonates who were born in Baghdad Teaching Hospital and 372 (37.2%) neonates who were born in other hospitals and referred to the Neonatal Care Unit of Children Welfare Teaching Hospital, medical city. Neonates with respiratory distress who were started on CPAP with bi-nasal prongswere studied. Maternal variables included multiple pregnancy, pregnancy induced hypertension, diabetes mellitus cesarean section and antenatal steroids.Infant variables included gender,birth weight, gestational age, surfactant use, chest X-ray, Fraction of inspired oxygen requirement, duration of hospital stay and CPAP use and mortality.*
Results:*Total number of pneumothorax was 78 (7.8%).The highest prevalence rate of pneumothorax was found in gestational age <28 weeks group 6 (16.7%),(P<0.001), and was highest among the elective caesarean 41(10.2%), but there was not statistically significant (P 0.058).The most common indications for use of CPAPwas RDS in (44.9%) and then meconium aspiration (21.7%) (p<0.001).PEEP with a pressure of 5 cm H2O was associated with increased risk of pneumothorax (p 0.001). The conventional type of CPAP was associated with more frequent cases of pneumothorax (p<0.001).The CPAP starting time and duration of the use of CPAP were significantly associated with pneumothorax (P<0.001). According to logistic regression analysis, Gestational age at birth (OR = 0.074, P 0.034) and duration of use of CPAP show significant role in the development of pneumothorax (OR = 2.086, P<0.001).*
Conclusions: *The risk factors which increased CPAP associated pneumothorax include preterm neonate with G.A≤28 weeks, late CPAP use and prolonged use of CPAP*
Keywords:*Neonates, Continuous positive airway pressure, Pneumothorax*

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I. Introduction

Continuous positive airway pressure (CPAP) has been used in preterm babies, full term babies and meconium aspiration as a mode of respiratory support since the 1970s and is now used in most NICUs in the world (1-5).Pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, pneumatocele, and vascular air embolism have been described in infants receiving CPAP.(6)Pneumothorax is one of the most common air leak syndromes that occur in newborn than any other time in life. Symptomatic pneumothorax occurs in 0.08% of all live births (7)and in 5% to 7% of infants with birth weight of less than 1500 grams(8).

The risk for pneumothorax is higher in infants with respiratory distress syndrome, meconium aspiration syndrome, and pulmonary hypoplasia and in infants who need resuscitation at birth. CPAP and positive pressure ventilation further increase the incidence of pneumothorax (9). Surfactant, use of synchronized or volume guarantee ventilation, and high-rate, low-tidal-volume ventilation decrease the incidence of pneumothorax (10).
The infants on ventilatory support, such as preterm infants and infants with underlying pulmonary disease, have an increased risk of developing one of the air leak syndromes. Various reports have indicated an incidence as high as 41%, and as low as 9% for infants receiving some form of mechanical ventilator assistance.(11)

The aim is to study the maternal and neonatal risk factors for the development of pneumothorax following the use of CPAP in any baby with respiratory distress in NCU of Children Welfare Teaching Hospital and Baghdad teaching hospital, Medical City Complex, Baghdad.

II. Patients And Methods

This descriptive prospective analytic study was conducted on neonates who needed CPAP for respiratory distress and who were admitted to Baghdad teaching hospital and children Welfare Teaching Hospital, Medical City, Baghdad, during the period from March 15, 2014 to March 15, 2015.This study includes 1000 registered neonates: 628 (62.8%) neonates who were born in maternity Baghdad Teaching Hospital and 372 (37.2%) neonates who were born in other hospitals and referred to the NCU of Children Welfare Teaching Hospital, medical city.Data collection based on maternal and infant variables: the maternal variables included parity, multiple births, premature rupture of membranes, meconium aspiration syndrome, mode of delivery (cesarean section or spontaneous vaginal delivery), pregnancy risk factors (hypertension, diabetes mellitus) and antenatal steroids used which used before delivery for fetal lung maturation. The infant variables included Sex, birth weight, gestational age, chest X-ray, FiO_2 requirement. The gestational age was calculated on mothers` last menstrual period and or early pregnancy ultrasound scan or New Ballard score (Ballard scoring system: in which estimation of gestational age by physical examination by assessment of physical and neurological criteria of maturity. It is accurate to ±2 weeks)(12).The other clinical data were recorded; the age of neonates when CPAP had been started, duration of CPAP used and PEEP level.

Inclusion criteria: All the registered neonates received CPAP in NCU (neonatal care unit) of both hospitals according to the following criteria:

1. Severe birth asphyxia 2. Respiratory distress syndrome (RDS) diagnosed clinically and by chest X-ray 3. Transient tachypnea of the Newborn (TTN) 4. Meconium aspiration syndrome. 5. Post extubating

Exclusion criteria**:**1. Major congenital anomalies (heart, GIT, CNS, skeletal, renal, etc.). 2. Overwhelming infection despite surfactant administration and CPAP use. 3. Neonates with sepsis. 4. Neonates referred from other hospital that already had pneumothorax. 5. Patients who were put on CPAP then transferred to mechanical ventilator.6. Patient equal or less than 24 weeks of gestation as they are considered abortion and usually died immediately.

All neonates were put on either Bubble NCPAP (Fisher and Paykel Health care , New Zealand), or CPAP (SLE 2000, U.K).The CPAP is used with bi-nasal prongs, PEEP was started at 4-5 cm of H2O and adjusted to minimize chest retractions. FiO2 was adjusted to maintain SpO2 between 87% and 95 %. Bubble CPAP was considered to be successful if the respiratory distress improved and the baby could be successfully weaned off from CPAP. The criteria for weaning were absence of respiratory distress (minimal, no retractions, respiratory rate between 30 and 60 per minute), SpO2 >90% on FiO2 <30% and PEEP <5 cm of water(13).

For patients who need surfactant prophylactic and therapeutic, we used animal-derived Beractant (Survanta) minced bovine lung extract. We use the practice of intubation, administering surfactant replacement (10– 15 min.), with immediate extubation and short-term (usually < 1 hr.) (INSURE)(14).

We follow American academy guidelines; committee on fetus and newborn regarding the indications for surfactant administration including:

Preterm infant with clinical RDS especially in those with low gestational ages and birth weights, radiological evidence of RDS as fine reticulogranular appearance and air bronchogram on chest x-ray, and those with high FIO2 need > 40% of inspired oxygen to maintain appropriate arterial pressure (15).

III. Statistical analysis

Each patient assigned a serial identification number. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 20. The categorical data presented as frequency and percentages. Pearson's chi-square test was used to test the association between the categorical data. Student t-test parametric and Mann-Whitney U non-parametric tests were used according to the type of distribution to compare between the continuous variables. Logistic regression was used to assess the effect of some factors among the included neonates that leads to Pneumothorax. The level of significance in this study was of p – value less than 0.05.

IV. Results

Total number of pneumothorax in this study was 78 (7.8%).There was no significant association between the gestational number of fetuses and the presence of pneumothorax as it was present among 71 (8.3%) of the singleton and 7 (4.9%) of the twins (P value of 0.155). Table1The highest prevalence of pneumothorax was among the gestational age <28 weeks group 6 (16.7%) in comparison to1 (0.9%) among 28 – 32 weeks group, thus there was significant association between the gestational age group and pneumothorax (p value<0.001). Table 1Pneumothorax was higher among elective caesarean section group 41 (10.2%) in comparison to 26(6.4%) emergency caesarean section group and 11(5.6%) spontaneous vaginal delivery group. Despite this difference, there was no significant association between the pneumothorax and the mode of delivery

(P value of 0.058) .Table 1The gender also did not show a significant association with the pneumothorax as 51(8.4%) of the males and 27(6.9%) of the females were diagnosed with pneumothorax (p Value of 0.368) (table 1).

Table 1: Gestational numberof fetuses and delivery characters according to the presence of Pneumothorax, n=1000.

Variables	Pneumothorax No. (%)		Total	p-value
	Yes	No		
Gestation number				
Singleton	71 (8.3)	785 (91.7)	856	0.155
Twin	7 (4.9)	137 (95.1)	144	
Gestational age at delivery				
<28 weeks	6 (16.7)	30 (83.3)	36	<0.001*
28 - 32 weeks	1 (0.9)	115 (99.1)	116	
32 - 37 weeks	16 (3.9)	398 (96.1)	414	
> 37 weeks	55 (12.7)	379 (87.3)	434	
Mode of delivery				
Spontaneous vaginal delivery	11 (5.6)	185 (94.4)	196	0.058
Elective caesarean section	41(10.2)	359 (89.8)	400	
Emergency caesarean section	26 (6.4)	378 (93.6)	404	
Gender of the fetus				
Male	51 (8.4)	555 (91.6)	606	0.368
Female	27 (6.9)	367 (93.1)	394	
Chi-square test, * significant at the 0.05 level.				

Neither maternal usage of steroid nor the presence of maternal risk factors during the pregnancy had significant associations with pneumothorax (P value of 0.206, 0.083). Table 2

Table 2: Antenatal maternal steroid use and risk factors during pregnancy n=1000.

Variables	**Pneumothorax No. (%)**		**Total**	**p-value**
	Yes	No		
Maternal usage of steroid				
No	47 (8.8)	487 (91.2)	534	0.206
Yes	31 (6.7)	435 (93.3)	466	
Risk factors				
No	65 (8.6)	687 (91.4)	752	0.083
Yes	13 (5.2)	235 (94.8)	248	
*** Significant at the 0.05 level.**				

The administration of surfactant was not associated with significant decrease in the prevalence of pneumothorax (P value 0.461). The most common indications for CPAP that was significantly associated with the presence of pneumothorax was RDS in (44.9%) and then meconium aspiration (21.7%) (p<0.001). The level of Positive end-expiratory pressure (PEEP) with pressure of 5 cm H_2O was significantly associated with more prevalence of pneumothorax as compared to those used 4 cm H_2O pressure type (p=0.001). SLE type of CPAP was significantly associated (p=0.001) with more frequent cases of pneumothorax (12.6%) as compared to Bubble type (5%), <0.001. Table 3

Table 3: Relation between resuscitation's indications and procedures and the presence of Pneumothorax, n=1000.

Variables	Pneumothorax No. (%)		Total	p-value
	Yes	No		
Administration of surfactant				
No	66 (8.1)	749 (91.9)	815	0.461
Yes	12 (6.5)	173 (93.5)	185	
Continuous Positive Airway Pressure (CPAP) indications				
Apnea of prematurity	1 (1.7)	57 (98.3)	58	<0.001*
Meconium aspiration	17 (28.8)	42 (71.2)	59	
Post extubation	1 (2.0)	48 (98.0)	49	
RDS	35 (13.4)	227 (86.6)	262	
TTN	24 (4.2)	548 (95.8)	572	
Positive end-expiratory pressure (PEEP)level				
4 cm H_2O	38 (5.8)	616 (94.2)	654	0.001*
5 cm H_2O	40 (11.6)	306 (88.4)	346	
Type of Continuous Positive Airway Pressure (CPAP)				
Bubble CPAP	32 (5.0)	604 (95.0)	636	<0.001*
Conventional CPAP	46 (12.6)	318 (87.4)	364	
*** significant at 0.05 level**				

The average birth-weight of neonates with pneumothorax was (2500 ± 670) grams and that with no pneumothorax was (2430 ± 720) grams, nevertheless no statistically significant difference was shown between them (P value of 0.455). The FIO2 in patients with pneumothorax was (59.2 ± 17.1), while those without pneumothorax was (57.6 ± 14.0), with no statistically significant difference (P value 0.32).

The median starting time and duration of the CPAP use were significantly longer (p<0.001) among patients with pneumothorax as they started CPAP late (5 hours)and stay for 5 days in comparison to 2 hours for neonates without pneumothorax who remain for 3 days on CPAP. Table 4

Table 4: Comparison of birth-weight, CPAP using time, FIO2 concentration and duration of hospitalization according to presence of Pneumothorax, n=1000.

Variables	Pneumothorax		p-value
	Yes	No	
Birth-weight (g) Mean ± SD	2500 ± 670	2430 ± 720	0.455
Time of starting CPAP (hours) Median (IQR)	5 (2 - 20)	2 (1 - 6)	<0.001*
Oxygen concentration (FiO2) Mean ± SD	59.2 ± 17.1	57.6 ± 14.0	0.32
Duration of CPAP use (days) Median (IQR)	5 (4 - 7)	3 (3 - 5)	<0.001*
*** significant at the 0.05 level**			

As the total prevalence of pneumothorax was found to be 78 (7.8%), the highest percentage of patients was found in very low birth-weight neonates (10.2%), (2.6%) in BWT of 1500- 1999 g, (8.3%) in BWT of 2000- 2499 g, (8.8%) in neonates with birth-weight (2500-4000) grams , while none was found among extremely low birth-weight neonates. Using the logistic regression analysis, gestational age at delivery before 28^{th} weeks had significantly higher percentage of pneumothorax (OR=0.074, p=0.034). The duration of CPAP use was shown to be significantly longer by more than two days in neonates with pneumothorax compared to those with no pneumothorax (OR=2.086, p<0.001). CPAP indications, type of Positive end-expiratory pressure, type of CPAP and the starting time of using it did not show any significant role in development of pneumothorax. Table 5

Table 5: Logistic regression for evaluation of different factors for developing Pneumothorax, n=1000.

Variables	Regression coefficient (B)	p-value	Odds ratio (OR)	95% CI for OR	
				Lower	Upper
Gestational age					
28 - 32 weeks	-2.598	**0.034***	0.074	0.007	0.821
32 - 37 weeks	-0.124	0.884	0.883	0.166	4.69
> 37 weeks	1.711	0.065	5.537	0.9	34.064
Continuous Positive Airway Pressure (CPAP) indications					
Meconium aspiration	1.716	0.193	5.563	0.419	73.819
Post extubation	-0.913	0.606	0.401	0.012	12.893
RDS	1.978	0.108	7.225	0.649	80.454
TTN	0.734	0.574	2.084	0.161	26.994
PEEP type (5 cm H_2O)	0.507	0.101	1.66	0.906	3.04
SLE type of (CPAP)	1.687	0.125	5.403	0.628	46.519
Duration of CPAP use	0.735	**<0.001***	2.086	1.634	2.664
Time of using CPAP	0.018	0.149	1.018	0.994	1.043
Constant	-12.44	<0.001*	-	-	-

V. Discussion

Pneumothorax in newborn results in significant morbidityand mortality [(16)]; it may even increase chronic lung disease in VLBW neonates [(17)] and intraventricular hemorrhage in preterm neonates. CPAP is an alternative to Mechanical ventilation for management of RD in neonates and said to increase incidence of pneumothorax [(18)]. Total number of pneumothorax in this study was 78 (7.8%), while in ManojMalviya et al was 13 (13.8%) [(19)],their study was limited by the retrospective nature of the data and the lack of long-term developmental outcomes.There was no significant association between number of gestations and occurrence of pneumothorax (8.3% in singleton and 4.9% in twin, P value of 0.155) although the second twin baby is more liable for respiratory distress than the first one or than single one [(20)].

The occurrence of pneumothorax is more among extremely preterm as GA<28 weeks (16.7%),28-32(0.9%),32-37 (3.9%) and in>37 weeks (12.7%). These results agree with Morley et al[(21)]who found that CPAP increased the prevalence of pneumothorax of preterm infants, while Maria Wilinsket a1 [(22)] study foundpneumothorax in 3.1% in ages <28 weeks and 2.6% (28-32) , 3.8% (33-36) , 5%(> 36 weeks). The second high percentage of pneumothorax was among near term G.A may be because of less antenatal steroid taken by the mothers who reach term pregnancy and most of them were delivered by elective c/s.These results were comparable with Hishikawa K, et al [(23)] who found an increase incidence of pneumothorax in early-term neonates (95%).

There was no significant association between the pneumothorax and the mode of delivery. In Benterud Tet al [(24)] study among neonates delivered at moderately preterm (30-36 weeks) by CS, the prevalence of pneumothorax and other respiratory problems was significantly increased. In full term, 0.5% elective c/s and 0.6% emergency c/s and 0.1% in NVD have pneumothorax after use of CPAP. In preterm, there was no elective c/s but only emergency c/s (2.05%) and NVD (0.63%) and all had pneumothorax after use of CPAP.

There was no significant association between pneumothorax and gender as (8.4%) of the males and (6.9%) of the females were diagnosed with pneumothorax. Sandri et al.[(25)] found male infants were one of the risk factor of CPAP failure which may include pneumothorax.

The maternal use of steroid had no significant effect on the occurrence of pneumothorax. Henrik Verder H. et. al[(26)]found thatamong mothers who received two doses of antenatal steroid, the outcome in the early-treated group was better, but in the late-treated group the steroid effect was not evident.

Risk factors which include maternal hypertension and diabetes show no effect on occurrence of pneumothorax. The occurrence of gestational hypertension involves important perinatal implications such as prematurity, fetal growth restriction, and fetal distress. Although hypertension is believed to accelerate lung maturation, a study by the Brazilian Neonatal Network regarding risk factors for mortality in premature patients reported that hypertension was associated with increased risk of death [(27)].

The administration of surfactant was not associated with significant decrease in the prevalence of pneumothorax (6.5% had pneumothorax and 8.1% had no pneumothorax), this may be related to unavailability of surfactant and time of admission because some patient reach late to our center as they were referred late from private clinics or hospitals so they became out of time of benefit of surfactant, while Dani et al[(28)] found that with early surfactant and nCPAP administered , no pneumothorax result. The indications for CPAP significantly associated with the presence of pneumothorax as it was more prevalent among neonates who were presented with RDS (44.9%), this agrees with Koti et.al(29).PEEP with pressure 5cm H2O was significantly associated with more prevalence of pneumothorax (11.6%) as compared with those used 4cm H2O pressure (5.8%). In Hishikawa K, et al (23), the use of CPAP with 5–6 cmH2Owith monitoring of pressure by a manometer was not associated with pneumothorax, but sudden crying or fighting the CPAPor movement of the infant might have resulted in higher pressurein the alveoli than expected.

Conventional CPAP show significant association with occurrences of pneumothorax (12.6%) compared with Bubble CPCP (5%) and thisdifference may be related to newly used Conventional CPAP in our hospital with inadequate training of nursing staff and where used more in referred patients who came late with higher risk of developing pneumothorax .

The average birth weight of neonates with pneumothorax was (2500 ± 670)g and that with no pneumothorax was (2430 ± 720) gs, nevertheless no significant difference was shown between them (P value of 0.455), while in Fanaroff A.A. et .al(30), the incidence of pneumothoraxis 0.5-1% in term newborns (3067.9±4760.5 g) ,13% ininfants weighing 501-750 g, and 2% in infants weighing 1251-1500 g, and this difference in result may be related to including the gestational ages equal or < 24 weeks in their study (who are usually less than 750 gram at birth).

The starting time and duration of the CPAP use were significantly longer among patients with pneumothorax.Ceylanet al(31)found that early hospitalization and CPAP administration within less than 30 minutes will decrease the incidence of CPAP complications (3.2 ± 2.3) days. This occurs because majority of patients were delivered in other hospitals and referred too late, in addition to the limited capacity of our NICU with CPAP delivery systems.

As the total prevalence of pneumothorax was found to be (7.8%), the highest percentage of patients was found in (10.2%) of VLBW neonates 1.000 – 1499 g , (8.8%) of neonates with birth-weight 2500-4000g, while none was found among ELBW neonates because most of them either died after few hours or transferred to mechanical ventilator because of severe respiratory distress. Finer el .al explains that ELBW spend long time using mechanical ventilator if they use CPAP first and most of them will be intubated. (32)

Regarding gestational age at delivery, this study found that in comparison to those delivered before 28th weeks, neonates delivered 28 – 32 weeks had significantly lower percentage of pneumothorax, while the other age groups had no significant effects because the age group below 28 weeks stays shorter in hospital than (28 - 32) because they either died earlier or transferred to mechanical ventilator and then excluded from this study.

Conclusions: The risk factors which increased CPAP associated pneumothorax include preterm neonate with G.A≤28 weeks, late CPAP use and prolonged use of CPAP. We recommendsProper early CPAP use and setting, adequate follow up, regular monitoring, early weaning strategy from CPAP.

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Author's contributions: NNH participated in the study design, sequence alignment and drafting and finalization of the manuscript and submission to the journal. SHK participated in the study design, data collection, sequence alignment and drafting and finalization of the manuscript. All authors read and approved the final manuscript.

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