

## OBSERVATION ON NEONATAL APNOEA IN RELATION TO AETIOPATHOGENESIS AND THEIR OUTCOME

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### Abstract

**Background:** APNEA can be defined as cessation of breathing for longer than 20sec, or for shorter duration in presence of Bradycardia (Heart rate less than 100 beat/minute), cyanosis, Hypotonia or metabolic acidosis. **Materials and Methods:** The present random cross-sectional observational study was conducted on Neonates admitted in Neonatal Unit, Department of Pediatrics associated with Department of Physiology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga (Bihar), and Labor Unit, Department of Obstetrics and Gynecology, DMCH. Was done from March 2019 to September 2020. All babies having abdominal distention increased gastric aspirate and especially those with associated risk factor like respiratory distress, hypothermia, hypocalcaemia, hypoglycemia, birth asphyxia and feature of sepsis were included in the study. **Result:** Out of 500 Cases, 141 cases presented with Apnea. Out of 315 preterm babies (<37 gestational) only 140 (44.444%) presented with Apnea. Out of 315 preterm babies and 185 term babies only 140 cases (44.44%) and 1 case (0.5%) presented with Apnea. **Conclusion:** It is concluded that all babies  $\leq$  32 weeks gestation need to be closely monitored for Apnea. With increasing gestation age and weight, the survival rate increases and incidence of apnea decreases. About half of the cases are related to infection and one fourth to Apnea of prematurity.

## INTRODUCTION

About 30-45% of preterm neonates exhibit periodic breathing pattern characterized by three or more respiratory pause of greater than 3seconds duration. Periodic breathing is a normal event in preterm infants, reflecting immaturity of respiratory control system and does not merit any treatment. In contrast apnea is a pathological cessation of breathing that result in hemodynamic disturbances and requires treatment.<sup>[1]</sup>

APNEA can be defined as cessation of breathing for longer than 20sec, or for shorter duration in presence of Bradycardia (Heart rate less than 100 beat/minute), cyanosis, Hypotonia or metabolic acidosis.<sup>[2]</sup>

Bradycardia and cyanosis are usually present after 20 seconds and apnea may occur more rapidly in the small premature infant. After 30-45 seconds, Pallor and hypotonia are seen and infants may be unresponsive to tactile stimulation.<sup>[3]</sup>

APNEA can be defined statistically as respiratory pause that exceed 3 standard deviation of the mean breath time of an infant. Respiratory pause are more prevalent during sleep than during the waking state and more frequent, shorter in REM than quite sleep.<sup>[4]</sup>

Apneic spells occur very commonly in premature infants. The incidence increase with decreasing gestational age. It is obtained in almost 1/4th of all preterm babies weighing less than 1.8 kg, and gestational age < 34 weeks will have at least one apneic spell. The incident among babies weighing less than one kg approaches nearly 80 %.<sup>[5]</sup>

The spell generally begins at 1-2 days of age and change of getting spell after 7th day of postnatal life is very unlikely.

Severe premature babies need close monitoring. The apneic spell persists for variable postnatal period. The term babies are very less likely of getting apneic spells. If apnea is occurring at or near term babies, it is unlikely of idiopathic origin and is nearly always associated with serious identifiable cause like birth asphyxia, lateral ventricular hemorrhage, seizure, drug depression, or CNS structural abnormality.<sup>[6]</sup>

In nasal thermistor pneumocardiogram testing for six hours in preterm infant, it was observed that 70 % infants demonstrated either apnea, apnea with bradycardia or excessive periodic breathing for age and subsequently, required medical intervention suggesting that in the infant < 36 weeks of gestation there is an inherent immaturity of breathing control.<sup>[7]</sup>

It was previously thought that the central respiratory control mechanism and the peripheral receptors of premature infant were solely responsible for Apnea. As many infant have shown mixed apnea suggesting that the mechanism responsible for maintenance of airway patency may be inadequately developed in this population. In addition, preterm babies have compliant chest wall which further compromise their ability to maintain lung volume and airway tone.<sup>[8]</sup>

## MATERIALS AND METHODS

The present random cross-sectional observational study was conducted on Neonates admitted in Neonatal Unit, Department of Pediatrics associated with Department of Physiology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga (Bihar), and Labor Unit, Department of Obstetrics and Gynecology, DMCH. Was done from March 2019 to September 2020.

All babies having abdominal distention increased gastric aspirate and especially those with associated risk factor like respiratory distress, hypothermia, hypocalcaemia, hypoglycemia, birth asphyxia and feature of sepsis were included in the study.

### All the babies suspected of having the apnea were examined for the following:

1. Birth weight or weight on admission (babies born outside DMCH).
2. Sex of babies also recorded.
3. Approximate gestational age was known from the parent or guardian and also confirmed by Debowitz scoring system.
4. Evidence of birth Asphyxia by recording Apgar score at 1 minute after birth.
5. Evidence of Respiratory distress at time of admission.
6. Recording temperature and measuring the blood sugar, calcium and electrolyte.
7. Sepsis screening which included total leucocytes count, neutrophil count, immature neutrophil: total WBC count, blood culture, CSF culture in addition to clinical features of sepsis like lethargy, poor feeding.
8. All infant at risk of Apnea are monitored for initial 7 days of life with Apnea Monitor which alerts the respiration ceases.
9. Apnea of prematurity was diagnosed when entire work up was negative.

### Criteria for Diagnosis of Respiratory Distress:

1. Respiratory rate greater than 60/min.
2. Superasternal retraction.
3. Intercostal retraction.
4. Xyphoid retraction.
5. Subcostal suction.
6. Expiratory grunt.
7. Cyanosis in room air.

Of two or more than two of above-mentioned criteria were present on two consecutive examinations at

least 1 hour apart, a diagnosis of respiratory distress was made.

### Apgar Scoring for Evidence of Birth Asphyxia :

At the end of one minute after complete birth babies were routinely given a score considering five clinical signs.

Sign	0	1	2
Heart rate	Absent	Less than 100/min	More than 100/min
Respiration	Absent	Irregular and weak	Regular & good cry
Muscle tone	Flaccid	Some degree of flexion	Active movement
Reflex (or catheter in Nostril)	Absent	Grimace	Sneezing or crying
Color	Blue/Pale	Body pink & extremities blue	Totally pink

Severe asphyxia : 0-3

Moderate asphyxia : 4-6

### Practical epigram of apgar score:

Physical criterias of Dubowitz scoring system:

### Debowitz Scoring system for Estimation of Gestational Age :

This system is accurate to +2 weeks in estimating the gestational age. The system includes certain physical and neurological criteria's. The physical and neurological criteria score are totaled and plotted on a graph to estimate the gestational age.

### Monitoring

All infant at risk of Apnea including < 35 week of gestational age is to be monitored for initial 7 days of life by Apneometer till no significant episodes has been detected for at least 5 days. Evaluate history, physical examination, ABG, CBC, blood glucose, Ca<sup>++</sup> and electrolyte level.

### Apneic Monitor

The respiratory monitor based on impedance technique measures. Changes in three electrical resistances during breathing. The electrode is fixed on the chest wall to pick up signals which digitally displayed as respiratory rate. The respiratory exclusions can also be displayed on the oscilloscope. The conventional apnea monitors are based on air mattress having plethysmographic sensor. The mattress is placed underneath the chest of the infant are recovered and displayed. When infant stop breathing after a variable interval of 10 to 20 seconds depending upon the present lag, the instrument emit a bleep and displays red light warning signal.

## RESULTS

Out of 500 Cases, 141 cases presented with Apnea. Out of 315 preterm babies (<37 gestational) only 140 (44.44%) presented with Apnea. Out of 315 preterm babies and 185 term babies only 140 cases (44.44%) and 1 case (0.5%) presented with Apnea.

**Table 1: incidence of apnea in different age group**

Age	Number	APNEA	incidence
< 30 weeks	45	40	88.89
31-32 weeks	124	92	74.19
33-36 weeks	146	8	5.47
> 37 weeks	185	1	0.5

Total 500  
 Apnea 62  
 No of Premature baby 315  
 (Born before 2 weeks or completed 37 week)  
 Apnea in Premature baby 140  
 % of Apnea in Premature baby 44.444%

**Table 2: Sex Wise Distribution of Apnea**

Sex	Preterm	No. Of apneic cases	Percentage (%)
Male	165	73	44.24%
Female	150	68	45.33%

Out of total 315 cases of prematurity, 165 were male and 150 were female. Among these 73 cases (44.24%) and 68 cases (45.33%) presented with Apnea. Thus no sex predilection noticed.

Out of 330 LBW cases (< 2.5 Kg) and 170 babies of normal weight (> 2.5 kg), 139 cases (42.12%) and 2 cases (1.17%) presented with Apnea.

Out of 40 cases of (<1000 gm), only 34 (85%) presented with Apnea while 170 case of > 2.5 Kg group, Only 2 cases (1.1%) presented with Apnea. Out of 141 cases 107 cases of Apnea were recorded in day 2-7.

Out of total 141 cases, 104 cases (74%) presented on day 2-7. while 32 cases (22%) and 5 cases (4%) presented on day 1 and day > 7 respectively.

**Table 3: frequency distribution of different cause of apnea**

Cause	Number	Percentage
Infection	62	44
Apnea of Prematurity	45	32
Intraventricular hemorrhage	6	4
Birth asphyxia	5	4
Hyline membrane disease	3	2
Hypoglycemia	6	4
Seizure	3	2
Hypocalcemia	3	2
PDA with large shunt	3	2
Anesthesia	3	2
GE Reflux	1	1
Nasal Stenosis	1	1
Choanel atresia		
Vocal cord paralysis		

**Table 4: frequency distribution of different type of infection responsible for apnea**

Cause	Number	Percentage (%)
Infection	62	44
Septicemia	40	28
Meningitis	11	8
Shock	3	2
Necrotizing Enterocolitis	3	2
Pneumonia	5	4

**Table 5: frequency pattern of symptoms and signs in AOP (apnea of prematurity)**

Symptom and signs	No. of cases	Percentage (%)
Bradycardia	139	98.58
Cyanosis	130	92.19
Pallor	94	66.67
Hypotonia	56	39.71
Lethargy	58	41.13
Jitteriness	39	27.66
Feeding tolerance	86	86.141

Table shows bradycardia (< 100 bpm or 30 beat less than previous value) and Cyanosis are associated with almost all case of AOP.

**Table 6: outcome in relation to different gestational age**

Gestational age	Incidence	Survival	Percentage
< 30 weeks	40	9	22.72
31-32 weeks	92	59	64.13
33-36 weeks	8	7	87.5
> 37 weeks	1	1	100

Survival percentage improves with increased gestational age. It is 100% in > 37 weeks in present study.

## DISCUSSION

Incidence of apnea in preterm babies (weight less than 1.8 kg and gestational age less than 34 weeks) was 25% in study done by Uday Bodhankar et al (Advance Ped 1996).<sup>[9]</sup>

Multicentre study being conducted by the collaborative Home infant monitoring evaluation (CHIME) group found apnea of  $\geq 20$  sec in 31% of all infants and extreme event of apnea (duration  $\geq 30$  sec or Heart rate < 60 bpm) in additional 10% of infant. Later were common only.

Also Henderson-Senat found 78% of infant preterm babies born at 26-27 week, 75% at 28-29 week, 54% at 30-31 weeks 14 % at 32-33 weeks and 7% at 34-35 weeks suffered apneic attack.<sup>[10]</sup>

Thus above observations are similar to present observation with little difference in percentage.

In the present study the incidence of Apnea in babies less than 30 weeks of gestation was 88.89 per 100 live birth, those born at 31-32 week was 74.19 per 100 live birth, those born in between 33-36 week was 5.47 per 100 live birth and those born after 37 week was 0.5 per 100 live birth.<sup>[11]</sup>

Similarly out of 500 babies admitted 339 were of low birth weight (<2.5 kg) in which 139 case (42.12%) presented with apnea while out of total 130 case of babies having adequate birth weight (>2.5 kg) only 2 cases (1.17%) suffered from apnea. (Graph F and Table-6), while studying. Incidence of apnea in < 1000 gm, 1000-1499 gm, 1500-2499 gm and > 2500 gm are 85 %, 50%, 25% and 1.1% respectively.<sup>[12]</sup>

Apnea in premature babies may be due to developmental immaturity, which decreases over a period on which brain stem conduction time of auditory evoked response shortens as post conceptional age increases. Further the chemoreception response to hypoxia in preterm babies may lead to transient hyperventilation followed by hypoventilation and apnea. (Brady and Ceruti 1966). In addition to hypoxia, also may be responsible for depressed hypoxic ventilatory response (Koo and Matsuda, 1990).<sup>[13]</sup>

Chemoreceptor sensitivity to CO<sub>2</sub> increases progressively to adult value by full term (Riga HO 1977, Rigatto et al 1975) and by 2 week of postnatal age in small preterm infant (Legererantz, 1992).<sup>[14]</sup>

Also highly complaint chest wall and presence of intercostals phrenic inhibitory reflex activated by chest distorten predispose small premature infant to obstructive apnea. (Gerhardt and Bancalari 1984 b).<sup>[15]</sup>

Most apnea occur during active sleep (Schulte 1977). REM sleep pattern is more than 50% of sleep in small

premature infant and the mature amount of 20% is not reached until 6 month of age (Bryan and Bryan, 1986). In REM sleep, skeletal muscle tone of the pharynx and tongue is inhibited promoting obstruction in the upper air way may leading to apnea.<sup>[16]</sup>

There was no evidence of sex predilection in present series of work. 73 babies were male and 68 babies were female who have apnea. There were 165 male and 150 female preterm babies in total. Thus apneic cases were 44.24% and 45.33% in male and female sex respectively.<sup>[17]</sup>

In the present series of work one forty one (141) babies developed apnea. Apnea in thirty two babies occurred on Day one, one hundred four (104) babies had apnea on Day 2 to 7 and only 5 babies developed apnea after 7 days. So overall incidence of Apnea on Day 1, Day 2-7 and Day > 7 were 22, 74, and 4 percent per 100 live birth respectively. This finding is correlated with result of study done by A Narang et al (IP 1997) in which Apnea occurred on Day 1. Day 2-7 and Day > 7 was 23, 76 and 1.8 percent respectively.<sup>[18]</sup>

Also Carlo et al have shown that apnea onset may occur on the first day of life in neonate without respiratory distress syndrome. In maturity cases of apnea of prematurity because evident with first 48 hours of life (77% of infant) and almost all occurred within first week of life.<sup>[19]</sup>

The commonest cause of Apnea was infection (44 %) followed by Apnea of prematurity (32 %). This is close to the study done by A Narang et al (1977 IP), in which infection and Apnea of prematurity was responsible for 49 percent and 24.5 percent respectively.<sup>[20]</sup>

In infection group septicemia was commonest cause responsible for 28 percent of total case of Apnea followed by Meningitis (8%), pneumonia (4%), NEC (2%) and Shock (2%).<sup>[21]</sup> Such infection include staphylococcus epidermidis bacteremia associated with venous catheter, candida fungal sepsis associated with vaginal delivery and dexamethasone administration, and respiratory syncytial virus pneumonia associated with bronchopulmonary dysplasia and nosocomial spread.<sup>[22]</sup>

So in the present study seventy six percent of cases of Apnea were caused by Infection and prematurity. The rest twenty four percent caused by IVH (4%), birth Asphyxia (4%), Hyaline membrane disease (2%), Hypoglycemia (4%), Seizure (2%), Hypocalcemia (2%), PDA (2%), Anaesthesia (2%), GE Reflux (1%) and upper air way structural abnormalities life nasal stenosis, choanal atresia, vocal cord paralysis 1%.<sup>[23]</sup>

A comparison of important characteristic of the babies with two commonest cause of Apnea (Infection and prematurity) revealed that the Mean birth weight and gestational age were 1250±450 gm and 31.5 ±3.25 weeks for infection group and 1025±350 gm and 30 ±1.5 weeks for Apnea of prematurity.<sup>[24]</sup>

Out of 141 cases, Apnea of 1-2 episode occurred in 50 case (35.46%) while 91 babies (64.54%) has 3 or more episodes.

101 cases (32% of total preterm babies) suffered from conventional apneic event defined as apnea of duration ≥20 sec and/or bradycardia (<100 bpm) while Rest 39 case (12.38% of total preterm babies) had extreme events (duration ≥30 sec or HR <60 bpm). Later occur only in preterm infants.<sup>[23,24]</sup>

Bradycardia and cyanosis wre almost always associated with apnea. If apnea persist longer, pallor, hypotonia, latergy and jitterine also occur. Within 1 second of apnea, desaturatein occur and after at least 5 second, bradycardia occurs.<sup>[25]</sup>

76 babies (53.9%) survived out of 141case of apnea survival depends on etiology and timely intervention. While comparing survival in apnea due to different cases, 31 babies (68.75%) survived out of 45 babies suffering from apnea of prematurity. This survival rate is only 32.25% in apnea due to infection as only 20 babies out of 45 babies suffering from apnea due to infection.<sup>[22]</sup>

Similar study done by A. Narang et al (1997 IP) shows that survival rate for babies in infection group and apnea of prematurity was 23 percent and 69.3 percent respectively.

In the present study Apnea due to Hylline membrane disease and seizure, the survival rate was negligible. Babies who developed apnea due to Hypocalcemia survived 100 percent but in Hypoglycemic group there was only 75 percent babies survived.

Using a definition of 20 second Henderson-Smart reported an incidence of Apnea of 78 % in infant born at 26-27 weeks of gestation, 75 percent at 28-29 weeks, 54 percent at 30-31 weeks, 14 percent at 32-33 weeks, and 7 percent at 34-35 weeks. The incidence in the present study also increased with decreasing gestational age and weight.

Apnea of prematurity generally begins at 1 or 2 days of life and if it does not occur during the first seven days it is unlikely to occur later.

Apnea which occurred at or near term, it is unlikely of idiopathic origin and in nearly always associated with serious identifiable cause which may have varied aetiology like respiratory (Hyaline membrane disease, pulmonary hemorrhage), metabolic (Hypoglycemia, Hypocalcemia, Hypernatremia), cardiovascular (Shock, PDA icefd) or CNS condition and if these condition are identified at appropriate time and early intervention in regard to varied aetiology is done, it will likely too reduce the Apneic spell lead to better survival of the babies.

As oxygen hood interferes with access to the infant, nasal canula is preferred to administered oxygen at flow of 1.2 l/minutes to maintain pulse oximeter

reading in the range of 92% to 96 % saturation. In comparison to oxygen hood, nasal canula may lead to chest wall distortion with less asynchrony between chest and abdomen. (Locke et al 1993).<sup>[25]</sup>

Most infant are treated with methylxanthines. As caffeine produces less tachycardia, has more favorable therapeutic index and produces less erotic blood fluctuation. These drug should be given for 2 weeks and then stopped to observe spontaneous cessation of apnea and if required should be continue for up to 38th week.

## CONCLUSION

It is concluded that all babies ≤ 32 weeks gestation need to be closely monitored for Apnea. With increasing gestation age and weight, the survival rate increases and incidence of apnea decreases. About half of the cases are related to infection and one fourth to Apnea of prematurity. Apnea of prematurity does not alter the outcome and majority can be managed without ventilation. Apnea occurring in association with sepsis however carries a poor prognosis and about more than half of these need ventilatory support. Once the infection is diagnosed, rigorous antibiotic therapy, maintenance fluid and electrolyte balance if apnea is persisting then proper ventilatory support may reduce the morbidity in a significant way.

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