

## Original Research Article

# Observation on neonatal apnea in relation to aetiopathogenesis and their outcome

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**Received:** 13 December 2016

**Accepted:** 15 December 2016

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### ABSTRACT

**Background:** Apnea is nearly universal among preterm infants, but neither the apnea burden nor its clinical associations have been systematically studied. This study was aimed to estimate the frequency of apnea in newborn, at different gestational age and birth weight and establish different etiological factors of apnea in newborn and their outcome.

**Methods:** The present study was conducted on neonates admitted in Special Newborn Care Unit, Department of Pediatrics, MGM Medical College and LSK Hospital, Kishanganj, Bihar, India between April, 2014 to September, 2016. All neonates at risk of apnea (< 34 weeks gestation) were monitored for at least the first week of life. Only neonates who developed apnea were included in this study.

**Results:** Out of 1275 newborns admitted in special newborn care unit, 637 were preterm and 98 newborns were diagnosed as having apnea- 96 were preterm and 2 were term. The frequency of apnea in babies  $\leq 30$  weeks was 45.91 per 100 live births. It gradually decreased to 13.45, 5.30 and 0.31 per 100 live births in newborn aged 31-32 weeks, 33-36 weeks and  $\geq 37$  weeks respectively (statistically significant, p value < 0.001). The frequency of apnea in babies whose weight was less than 1000 gm, between 1000-1499 gm, 1500-2499 gm and > 2500 gm was 38.88, 15.09, 6.45 and 0.49 per 100 live births respectively (statistically significant, p value < 0.001). In our study commonest causes of apnea was infection (51.02%) and apnea of prematurity (29.59%) (Statistically significant, p value < 0.001). The mean birth weight and gestation were 1434.34gm and 31.6 weeks for the infection group and 1117.41gm and 30.34 weeks for the apnea of prematurity group in our study. The survival rate in babies with apnea of prematurity was 72.41% (p < 0.001) as compared to 32% (P < 0.001) in apnea due to infection group. The percentage of survival in < 1000 gm, 1000-1499 gm, 1500-2499 gm and 2500gm was 22.85, 55, 60 and 100 percent respectively (p value < 0.001).

**Conclusions:** Infection and apnea of prematurity are common causes of apnea in newborn. All babies  $\leq 32$  weeks gestation needs to be closely monitored for apnea. Apneic spells occurring in infants at or near term are always abnormal and are nearly always associated with serious causes. Apnea due to sepsis carries a poor prognosis.

**Keywords:** Apnea, Apnea of prematurity, Neonatal sepsis, Low birth weight, Preterm

### INTRODUCTION

Apnea intervals frequently occur in premature infants. Periods of apnea occur more often with decreases in gestational age. Periods of apnea can cause damage to the

infant's developing brain and other organs.<sup>1</sup> These episodes can lead to hypoxaemia and bradycardia, which may be severe enough to require the use of positive pressure ventilation.<sup>2</sup> Most neonates who are born at a gestational age <29 weeks or a birth weight <1,000 g

experience apnea of prematurity.<sup>3</sup> Apnea, which is defined as pauses in their breathing pattern. Apnea of prematurity is often defined as a cessation of breathing that lasts for at least 20 seconds or at least 10 seconds followed by bradycardia and hypoxemia.<sup>4</sup> Although the pathophysiology of AOP is poorly understood, it is often attributed to immature respiratory control mechanisms.<sup>5,6</sup> Apnea of prematurity is a specific diagnosis and usually resolves between 34 to 36 weeks post conceptual age. The spell generally begins at 1-2 day of age and chance of getting spell after 7<sup>th</sup> day of post natal life is very unlikely. Sepsis is also an important cause of neonatal apnea. Sepsis is more common in preterm infants and low birth weight infants and has high incidence rates of apnea.<sup>7</sup>

## METHODS

The present study was conducted on neonates admitted in special newborn care unit, Department of Pediatrics, M.G.M. Medical College and L.S.K. Hospital, Kishanganj, Bihar, India between April, 2014 to September, 2016.

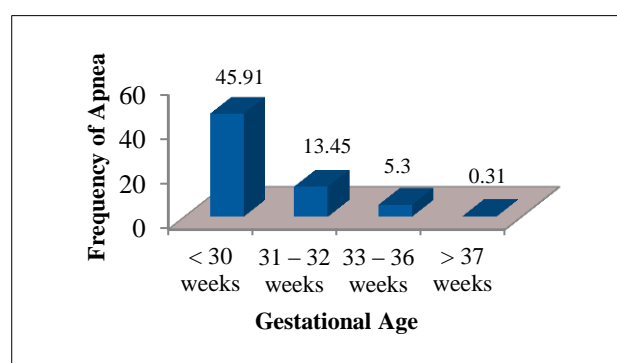
The gestational age and birth weight of all neonates were recorded. All neonates at risk of apnea were monitored for at least the first week of life. Only neonates who developed apnea were included in this study. After emergency treatment and stabilization, all the babies with apnea were examined for the- history, birth weight and sex, approximate gestational age (modified Dubowitz Ballard score), evidence of birth asphyxia, evidence of respiratory distress and features of neonatal sepsis. Detailed clinical examination of all neonates with apnea, was done with particular attention to temperature instability, jaundice, pallor, cardiac murmur, poor perfusion, seizures, jitteriness and neurological examination. Investigations like septic screen, Chest X-ray, blood glucose level, serum calcium and sodium, CSF examination, Urine examination and culture, CBC, arterial blood gas, USG head, ECG/Echocardiography were done to exclude common causes of secondary apnea.

Apnea of prematurity is a diagnosis of exclusion. All the babies who developed apnea were monitored for at least the first week of life or till absence of apneic episodes for at least 7 days. Monitoring was done for respiratory activity, heart rate and oxygen saturation by advanced apnea monitor integrated with pulse oximeter. The day of onset of apnea and number of apneic episodes were recorded for each baby. General measures like tactile stimulation, avoidance of vigorous suctioning of oropharynx, blood transfusion if hematocrit was <30%, treatment of underlying cause and specific measures for apnea like aminophylline and nasal continuous positive airway pressure were the treatment given. Aminophylline was the only drug which was used.

Though, caffeine is the drug of choice now, it was not used due to various constraints viz. non availability in our hospital. A loading dose of aminophylline in a dose of 5 - 7 mg/kg was administered intravenously followed by a maintenance dose of 1.5 - 2.0 mg/kg/dose IV every 8 hourly. Aminophylline was continued till 34 weeks corrected gestational age and stopped thereafter if no episodes of apnea have occurred in the last 7 days. The indication of Nasal CPAP was failure to respond to aminophylline therapy.

## RESULTS

Out of 1275 newborns admitted in Special Newborn Care Unit, 637 were preterm and 98 newborns were diagnosed as having apnea- 96 were preterm (15.07%) and 2 were term. The frequency of apnea in babies  $\leq 30$  weeks was 45.91 per 100 live births. It gradually decreased to 13.45, 5.30 and 0.31 per 100 live births in newborn aged 31-32 weeks, 33-36 weeks and  $\geq 37$  weeks respectively, as shown in Figure 1 (statistically significant, p value <0.001).



**Figure 1. Frequency of apnea in different gestational age groups.**

The frequency of apnea in babies whose weight was less than 1000 gm, between 1000-1499 gm, 1500-2499 gm and > 2500 gm was 38.88, 15.09, 6.45 and 0.49 per 100 live births respectively, figure 2 (statistically significant, p value < 0.001).

Out of 98 babies developed apnea, 20 babies developed apnea on day one, 76 babies on day 2-7 and 2 babies developed apnea after 7 days (Table 1). All the cases of apnea of prematurity developed apnea on day 2-7. Out of 98 newborns having apnea, 64.28% had  $\geq 3$  episodes, (p < 0.001) (Table 2).

**Table 1: Day of onset of apnea.**

Days	Frequency of apnea	Percentage
Day 1	20	19.38
Day 2 - 7	76	77.55 (p value <0.001)
Day > 7	02	2.04

In our study commonest causes of apnea were infection (51.02%) and apnea of prematurity (29.59%), The mean birth weight and gestation were 1434.34gm and 31.6 weeks for the infection group and 1117.41gm and 30.34 weeks for the apnea of prematurity group in our study.

The survival rate in babies with apnea of prematurity was 72.41% ( $p < 0.001$ ) as compared to 32% ( $P < 0.001$ ) in apnea due to infection group (Table 3).

**Table 2: Number of episodes of apnea.**

Birth weight	Frequency of apnea	Episodes of apnea	
		1 - 2	$\geq 3$
< 1000 gm	35	9	26
100 - 1499 gm	40	16	24
1500 - 2499 gm	20	7	13
$\geq 2500$ gm	03	3	0

**Table 3: Outcome in relation to aetiology of apnea.**

Aetiology	Number	Survive	Percentage
Infection	50	16	32.00 <sup>a</sup>
Apnea of prematurity	29	21	72.41 <sup>b</sup>
Birth asphyxia	05	02	40.00
Hyaline membrane disease	02	0	0
Intraventricular hemorrhage	03	01	33.33
Hypoglycemia	05	03	60.00
Seizure	02	0	0
Hypocalcemia	02	02	100

a t-4.85,  $p < 0.001$ , b t-8.72,  $p < 0.001$

**Table 4: Outcome in relation to different birth weight group.**

Birth weight	Frequency	Survival	Percentage	t value	p value
< 1000 gm	35	08	22.85	3.22	<0.001
1000-1499 gm	40	22	55	6.99	<0.001
1500-2499 gm	20	12	60	5.48	<0.001
$\geq 2500$ gm	03	03	100		

**Table 5: Outcome in relation to different gestational age.**

Gestational age	Frequency	Survival	Percentage	t value	p value
< 30 weeks	45	12	26.66	4.04	<0.001
31-32 weeks	37	20	54.05	6.60	<0.001
33-36 weeks	14	11	78.57	7.16	<0.001
> 37 weeks	02	02	100		

The percentage of survival in < 1000gm, 1000-1499 gm, 1500-2499 gm and  $\geq 2500$  gm was 22.85, 55, 60 and 100 percent respectively ( $p$  value < 0.001) (Table 4).

The percentage of survival in  $\leq 30$  weeks, 31-32 weeks, 33-36 weeks and  $\geq 37$  week was 26.66, 54.05, 78.57 and 100 percent respectively ( $P < 0.0001$ ) (Table 5).

## DISCUSSION

This single center study had several unique features which were designed to estimate the frequency of apnea in newborn, at different gestational age and birth weight and establish different etiological factors of apnea in newborn and their outcome.

In our study we found that the frequency of apnea in babies  $\leq 30$  weeks was 45.91. It gradually decreased to 13.45, 5.30 and 0.31 per 100 live births in newborn aged 31-32 weeks, 33-36 weeks and  $\geq 37$  weeks respectively. (this proportion is statistically significant,  $< 0.001$ ), which were comparable to earlier studies.<sup>8</sup> In our study total number of low birth weight babies was 665 out of which 95 developed apnea, the frequency being 14.28 per 100 live borns. The frequency of apnea in babies whose weight was less than 1000 gm, between 1000-1499 gm, 1500-2499 gm and  $> 2500$  gm was 38.88, 15.09, 6.45 and 0.49 per 100 live births respectively which was statistically significant. The result was close to study by Narang A et al, but was lower as compared to study by Smart H et al.<sup>8,9</sup> The lower incidence of apneic

spells in our babies may be due to decreased survival of more immature babies and less admission. Santin RL et al, stated that apnea may occur during the post natal period in 25% of neonates who weigh less than 2500 gm at birth and in 84% of neonates who weigh less than 1000 gm.<sup>10</sup> The lower incidence of apnea in very low birth weight babies at our hospital in comparison to Santin RL et al. may be due to less survival and less admission of very low birth weight infants.<sup>10</sup> In one study, as many as 25% of all premature infants who weigh less than 1800 gm (about 34 weeks gestational age) have at least one apneic episode.<sup>10</sup>

The apnea of prematurity presents after 1-2 days of life and within the first 7 days. Apnea presenting within the first 24 hours or after 7 days of age is unlikely to be apnea of prematurity.<sup>11</sup> Most of the apnea episodes in apnea of prematurity in our study had occurred on day 2-7, which was similar to various investigators.<sup>12-14</sup>

In this study we found that 64.28% of newborns having apnea had  $\geq 3$  episodes. This finding correlates with observations done by Narang A et al, in whose study 37.7% newborns had only 1-2 episodes of apnea whereas 62.3% had three or more episodes.<sup>8</sup>

In this study commonest causes of apnea was infection (51.02%) and apnea of prematurity (29.59%), rest of the apneic episodes were caused by other diseases like birth asphyxia, hyaline membrane diseases, intraventricular hemorrhage, hypoglycemia, seizures and hypocalcemia, which were responsible for 5.10%, 2.04%, 3.06%, 5.10%, 2.04% and 2.40% respectively which are very similar to the study done by Narang A et al, 22% of infants with bacterial sepsis presented with apnea in a study on clinical signs of bacterial sepsis in 455 newborn infants studied at four medical centers.<sup>8,15</sup>

Similarly in a study, the presenting features of first episode of septicemia was apnea/bradycardia in 55% of total neonates with sepsis.<sup>16</sup>

These findings can be correlated with statement that "it is imperative that infection be definitively ruled out or diagnosed and treated in all cases of recurrent apnea events. This is an important part of clinical practice with premature infants".<sup>17</sup>

With standard treatment (treatment of secondary causes, aminophylline, bag and mask ventilation and/or nasal CPAP) the survival rate in babies with apnea of prematurity was 72.41% ( $p < 0.001$ ) as compared to 32% ( $P < 0.001$ ) in apnea due to infection group. The above finding were close to the study by Narang A et al where survival rate for babies in infection group and apnea of prematurity were 23.1% and 69.3% respectively.<sup>8</sup> Better survival rate in apnea of prematurity can be explained by the fact that unless severe, recurrent and refractory to therapy, apnea of prematurity does not alter an infant's prognosis.<sup>8,9</sup> As associated problems of intra-ventricular

hemorrhage, BPD and retinopathy of prematurity are critical determining the prognosis for apneic infants.<sup>12,13</sup>

Clinical manifestation of hypocalcemia include apnea, seizures, jitteriness, increased extensor tone, clonus, hyperreflexia, and stridor. Prognosis of neonatal tetany per se is good, most cases making full recovery without sequelae.<sup>18,19</sup> In our study hypocalcemia was associated with 2.04% of apnea and survival rate was 100%.

The survival of babies increased with increasing birth weight. The percentage of survival in  $< 1000$  gm, 1000-1499gm, 1500-2499gm and  $< 2500$  gm was 22.85, 55.60 and 100 percent respectively ( $P < 0.001$ ). In a study, 13.3, 73.6, 88.7, 97.5 percent survival in newborns weighing  $< 1000$  gm, 1000 - 1500 gm, 1500 - 1999 gm and 2000-2500 gm respectively.<sup>20</sup> The mortality in  $< 1000$  gm in our study was comparable with this study. The high mortality in our study in newborn  $> 1000$  gm may be due to associated comorbidity.

Similarly as gestational age increases the survival rate also increased. The percentage of survival in  $\leq 30$  weeks, 31-32 weeks, 33-36 weeks and  $\geq 37$  week was 26.66, 54.05, 78.57 and 100 percent respectively ( $P < 0.0001$ ). In a study 0, 60, 63.2, 87.1 percent survival was observed in newborn aged  $< 28$ , 29-30, 31-32, 33-34 weeks respectively.<sup>21</sup> The findings in our study are comparable in newborn  $\leq 32$  weeks with the above study. A higher mortality in newborn  $> 32$  weeks may be due to associated comorbidity.

## CONCLUSION

As the maturity increases (increasing gestational age), the frequency of apnea decreases. The same is true for birth weight. Most of the apnea occurred on day 2-7. Infection was the most common cause of apnea; apnea of prematurity was second most common cause of apnea in newborn. Other important cause of apnea in newborn was birth asphyxia, hyaline membrane disease, intraventricular haemorrhage, hypoglycemia, seizure and hypocalcaemia. Survival rate increased as the gestational age of newborn increased. As birth weight decreases, survival rate of newborn decreased. The survival rate for babies in apnea of prematurity group (72.41%) was better than babies with infection (32%).

It is concluded that all babies  $\leq 32$  weeks gestation need to be closely monitored for apnea. Apneic spells occurring in infants at or near term are always abnormal and are nearly always associated with serious, identifiable causes. Infection is the most common cause of apnea and carries a poor prognosis. Apnea of prematurity which constitutes the second most common cause of apnea does not alter the outcome. So infection must be ruled out or diagnosed and treated in all cases of recurrent apnea. As apnea may be a manifestation of severe sepsis and any delay in diagnosis and initiation of treatment may result in death of the infant.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Kumar S, Nayanam S. Observation on neonatal apnea in relation to aetiopathogenesis and their outcome. *Int J Contemp Pediatr* 2017;4:249-53.