Original Research Article

A study on neonatal apnea in relation to etiopathogenesis and their outcome in a rural based Medical College Hospital;West Bengal; India

Pal A. C [1], Jha R.K. [2], Bandyopadhyay S [3], Chakraborti S [4], Mandal R. K.[5], Ali S [6]

[1]Dr Abhay Charan Pal, Associate Professor, [2]Dr Rajiv Kumar Jha, Post Graduate Trainee, [3]Dr Sudipta Bandyopadhyay, Post Graduate Trainee, [4]Dr Snehansu Chakraborti, Professor and HOD, above all authors are attached with Department of Pediatric Medicine, B.S Medical College, Bankura, West Bengal, India, [5]Dr Ramkrishna Mandal, Professor, Department of Surgery, B.S Medical College, Bankura, West Bengal, India, [6]Dr Sekendar Ali, Post Graduate Trainee, Department of Pediatric Medicine, B.S Medical College, Bankura, West Bengal, India.

Address for Correspondence: Dr Abhay Charan Pal, Subhankar Sarani, P.O.and Dist-Bankura, West Bengal; India, Pin:-722101, e-mail: abhaypal80@gmail.com

Abstract

Introduction: Neonatal apnea is one of the most common causes of Sick Newborn Care Unit and Neonatal Intensive Care Unit admission. Commonest etiologies of neonatal apnea include sepsis, apnea of prematurity, central nervous system insult, Respiratory distress Syndrome. **Background**: Apnea in neonates may be manifestation of many serious underlying diseases as well as may be due to prematurity. Apnea of prematurity is essentially a diagnosis of exclusion carries the most excellent prognosis. Other secondary causes bear uniformly poor prognosis and essentially high mortality. **Objectives**: This study was conducted in a tertiary care centre to determine the different causes of apnea and to observe the outcome in relation to different birth weight, gestational age and different etiologies. **Results:** Out of 110 apneic neonates recruited 60% had ≥ 3 episodes of apnea while 40% had 1-2 episodes. Sepsis and apnea of prematurity were found to be the two most common causes. Average birth weight and gestational age for the sepsis group was 1598·62 gm and 32·4 wks respectively whereas average birth weight and gestational age for apnea of prematurity group was 1094·07 gm and 30·0 wks respectively. Survival rate for babies with apnea of prematurity (71·42%) was better than babies with infection (42·3%). **Conclusion:** All babies born below 32 weeks of gestational age must undergo close monitoring for apnea. Neonates with apneic spells should be evaluated to exclude secondary causes of apnea like sepsis, hypoglycaemia and intracranial hemorrhage etc., because sepsis remains the commonest cause of apnea and carries a poor prognosis.

Keywords: Apnea of prematurity, Birth Weight, Cross-Sectional study, Gestational age, India, Neonatal apnea, Observational study, Sepsis

Introduction

Apnea is defined as cessation of breathing, Greek Word: Apnea – A- without, pnoea- breathing). Majority of premature neonates as well as some full term neonates have apnea [1]. As defined by the American Academy of Pediatrics apnea is an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor and/or marked hypotonia [2]. This should be distinguished from periodic breathing which is defined as periods of regular respiration followed by apneic spells lasting at least 3 seconds occurring for at least 3 episodes in succession [3].

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Apnea has traditionally been classified into three types namely central apnea (10-25%) defined as pause in diaphragmatic activity due to abnormality in central respiratory control mechanisms; obstructive apnea (12-20%) defined as pause in alveolar ventilation due to upper airway obstruction; and mixed apnea (almost 50%) defined as initial loss of respiratory drive accompanied by a superimposed delayed activation and/or closure of upper airway [4]. Apnea of prematurity is however a distinct entity and essentially a diagnosis of exclusion, usually occurring in preterm

neonates and commonly resolving between 34th to 36th weeks of post-conceptional age. Though not fully understood the mechanism of apnea of prematurity has been traditionally attributed to developmental central neuronal immaturity, decreased protective respiratory reflex, reduced sensibility of medullary chemoreceptor to sense co_2 level alteration and immature reflex response to peripheral vagal stimulation [4,5].

The fact that premature infants have recurrent apneic spells was well established by Miller and the association of recurrent apnea and high mortality was recorded by Reid and Tunstall[6].

Bradycardia is a reflex response observed in apnea, and is thought to be due to cessation of lung inflation , central brain stem depression and some cases may be due to hypoxemia [7,8]. Incidence and duration of apneic episodes increases with decreasing gestational maturity and birth weight and incidence of bradycardia increases with longer duration of apnea and obviously fall in oxygen saturation [9].

Chances of apnea decreases with increased gestational age, from 100% of those born at 23 weeks to almost 12% at 35 weeks [10]. Proposed mechanisms of apnea of prematurity are physiological immaturity of breathing control, altered central inhibitory neuromodulators like GABA and adenosine and lack of co-ordination of central respiratory rhythm generator in the brainstem [11-13].

Apart from apnea of prematurity(AOP) other important clinical conditions associated with apnea in preterm and also in fullterm neonates are pneumonia, Respiratory distress Syndrome(RDS), septicaemia, meningitis, hypoglycaemia, acidosis,seizures, intracranial hemorrhage, anemia, PDA, CCF as well as many others [6]. Apart from apnea of prematurity all the other attributable causes of apnea carries definitely worse prognosis.

Treatment of neonatal apnea constitutes of general measures like monitoring,use of a pulse oximeter, avoiding deep suctioning of pharynx and maintainance of optimum saturation between 88 and 92%[14]. Specific treatment includes management of underlying causes like packed cell transfusion,treatment of infection and treatment of other treatable specific conditions[15,16,18].

Management of apnea of prematurity constitutes of use of pulse oximeter,cutaneous stimulation,maintainance of prone position,methylxanthine or caffeine therapy and finally respiratory support by continuous positive airway pressure(CPAP), or by mechanical ventilation[17-24]. Caffeine has however been shown to be superior pharmacologial agent and has been traditionally recommended as the treatment of choice [21]. Overall mortality of neonates with apnea of prematurity reflects mostly underlying cause rather than apnea per se; and in some series it is upto 30% or more [25]. There may be no direct relationship between apnea and intellectual handicap(mental insufficiency) and the risk of occurrence of long term neurodevelopmental handicap as a result of neonatal AOP(apnea of prematurity) remains uncertain.

However prolonged apneic spell(s) and bradycardia with hypotension and consequent cerebral hypoperfusion can contribute to hypoxic-ischemic cerebral injury and subsequently mental insufficiency [26, 27]. Therefore this study was conducted in Sick Newborn Care Unit of a tertiary care Medical College Hospital to see the frequency of apnea in different gestational age and birth weight and to study different etiologies of apnea including apnea of prematurity.

Aims and objectives

1. To determine the causes of neonatal apnea and to estimate the occurrence of apnea in neonates of different gestational age-group and with different birth weight.

2. To determine the outcome of neonatal apnea with reference to gestational age and birth weight.

Materials

Study Design: Random cross-sectional observational study

Place and duration of study and setting: This study was conducted in SNCU and neonatal ward, Departmental of Pediatrics ; Bankura Sammilani Medical College and Hospital, Bankura, West Bengal, India. Study period extended from 1st June, 2014 to 31st May 2015

Data source: All admissions in SNCU and NICU during this period.

Participants: 110 neonates admitted into SNCU or neonatal ward who developed apnea and who were not post term.

Bias: There was no observer bias

Inclusion and exclusion criteria: Neonates who developed apnea were included in the study. Those neonates who were post term and not apneic were excluded. After stabilization and emergency management the babies with apnea were examined for gestational age-estimation (by history of LMP and modified Ballard Scoring), history of perinatal asphyxia, maternal drug ingestion and history of neonatal respiratory effort and history of resuscitation.

Study size: 110 neonates

Methods

Clinical examinations: Evidence of respiratory distress was examined for by noting respiratory rate, chest indrawing and expiratory grunt and evidence of neonatal sepsis like lethargy, poor cry, seizures, bulging fontanelle etc were looked for. Detailed clinical examination was performed to exclude or suspect temperature instability, jaundice, pallor, cardiac murmur, seizures, jitteriness or any other neurological abnormality.

Laboratory examinations: Laboratory workup was individualised and was intended to rule out common causes of secondary apnea as apnea of prematurity is largely a diagnosis of exclusion. Laboratory tests consisted of sepsis screen, chest Xray, blood glucose level, serum electrolytes, CSF examination, blood culture, haemoglobin, Arterial Blood Gas analysis, cranial sonography or MRI, ECG and Echocardiography as and when indicated.

Treatment and monitoring: All the cases underwent monitoring for at least the first week of life or till the absence of apnea for at least 7 days. Respiratory activity, heart rate and oxygen saturation were monitored by advanced apnea monitor and pulse oximeter.

The day of onset of apnea and number of apneic episodes were also recorded. Treatment of apneic neonates constituted of general measures like avoidance of vigorous oropharyngeal suctioning, tactile stimulation and bag-mask ventilation. Specific measures included treatment of underlying causes like sepsis, hypoglycaemia, seizures, hypocalcemia, anemia etc. Pharmacological agents included aminophyline,caffeine(drug of choice) and non-responding neonates were put on nasal CPAP or mechanical ventilation whenever warranted.

Caffeine, till date considered the drug of choice in treatment of neonatal apnea was administered in a loading dose of 20mg/kg body weight followed by 5-8mg/kg/dose q.24 hrs intravenously. Caffeine was continued till 34 weeks corrected gestational age and was stopped if no episodes of apnea occurred in preceding 7 days.

Statistical Methods: Data analysis was done using SPSS 20 for windows. Standard statistical tests were applied. Rates and proportions were calculated with 95% confidence intervals and level of significance was set at $p < 0.05$.

Permission from Institutional Ethics Committee: Necessary permission for conducting the study and to publish the results observed were obtained from the Institutional Ethics Committee of this college.

Analysis of Results and Observation

Table-1: Frequency and Day of onset of apnea in relation to birth weight

Birth weight	No of Baby	Onset of Apnea		
		Day1	Day 2-7	Day >7
<1000gm	35	7	28	0
1000-1499gm	45	7	37	1
1500-2499gm	27	5	20	2
≥2500 gm	03	1	2	0

Table-2: Day of onset of apnea

	No of baby developing Apnea	Percentage
Day 1	20	18.18
Day 2-7	86	78.18
Day>7	04	3.63

In our series 86 babies (n=110), i.e. 78·18% developed apnea between day 2 and day 7. All the cases of apnea of prematurity became apneic between day 2 and day 7.

Table-3 shows number of apneic episodes in the study population

Birth Weight	No of Baby with Apnea	Episodes of apnea	
		1-2 episode	≥ 3 episodes
<1000 gm	35	9	26
1000-1499gm	45	20	25
1500-2499gm	27	12	15
≥2500gm	03	3	0
Total	110	44	66

In the present study 66 neonates i.e. 60·0% of the recruited neonates has ≥3 episodes of apneic spells.

Table-4: Causes of apnea in our study population

Aetiology	Number	Percentage
Infection	52	47.27
Apnea of Prematurity	28	25.45
Birth Asphyxia	03	2.72
Respiratory distress Syndrome	09	8.18
Intraventicular hemorrhage	06	5.45
Hypoglycemia	06	5.45
Seizure	02	1.81
Hypocalcemia	01	0.90
Anemia	02	1.81
PDA	01	0.90

In our study commonest cause of apnea in neonates was infection (47.27%) and apnea of prematurity(25.45%), followed by RDS(8.18%), hypoglycaemia(5.45%), intraventricular hemorrhage(5.45%).

Table-5: demonstrates comparison between infection and apnea of prematurity in relation to birth weight and gestational age

Infection	Gestational Age	32.44±2.39 week
	Birth Weight	1598.62±559.9 gm
Apnea of Prematurity	Gestational Age	30.0± 1.17 week
	Birth Weight	1094.07±189.8 gm

Table-6: Shows outcome of neonates with apnea in relation to the etiology

Aetiology	Number	Survival	Percentage
1.Infection	52	22	42.30
2.Apnea of Prematurity	28	20	71.42
3.Birth Asphyxia	03	01	33.33
4.Respiratory Distress Syndrome	09	02	22.2
5.Intraventricular hemorrhage	06	02	33.33
6.Hypoglycemia	06	04	66.6
7.Seizure	02	0	0
8.Hypocalcemia	01	01	100
9.Anemia	02	02	100
10.PDA	01	0	0

Our study shows that with standard treatment i.e. treatment of secondary causes, caffeine, low level nasal CPAP (4 to 6 mm of H_2O), bag mask ventilation and other measures ; the survival rates of neonates with ' apnea of prematurity was 71.42% as compared to 42.30 in apnea due to infection group. The outcome is statistically significant.

Table-7: Explores the outcome of the study population in relation to different birth weight group

Birth Weight	No of Baby	Survival	Percentage
<1000 gm	35	08	22.85
1000-1499 gm	45	25	55.5
1500-2499 gm	27	18	66.6
≥2500 gm	03	03	100

In our series we found that survival increases with increasing birth weight.The percentage of survival in <1000gm,1000-1499 gm,1500-2499 gm and ≥2500 gm was 22.85,55.5,66.6 and 100 percent respectively($p<0.001$).

However it is speculated that high mortality in newborn >1000gm in our study may be due to associated comorbidity.

Table-8: Shows the outcome of the neonates in relation to different gestational age

Gestationl Age	No of Baby	Survival	Percentage
≤30 weeks	45	12	26.66
31-32 weeks	37	19	51.35
33-36 weeks	25	20	80.0
≥37 weeks	03	03	100

Table 1 and Table 2 shows frequency and day of onset of apnea in neonates with different birth weight.

A comparison of the important characteristics of the neonates with the two commonest causes of apnea namely infection and apnea of prematurity revealed that mean birth weight and gestational age were 1598.36±559.9 gm and 32.44±2.39 weeks for the infection group and 1094.07±189.8 gm and 30.0±1.17 weeks for the apnea of prematurity group respectively in our study.

It was seen in our study that as gestational age increases, survival rate also increases.Our series showed that percentage of survival in ≤30 weeks,31-32 weeks,33-36 weeks and ≥37 weeks was 26.66,51.35,80.0 and 100 percent respectively($p<0.0001$)

Discussion

In the present series out of 2980 newborns admitted in the Sick Newborn Care Unit and Neonatal Intensive Care Unit, Bankura Sammilani Medical College and Hospital during the study period, 147 newborns developed apnea out of which 110 cases were recruited randomly.

In our study 86 neonates (i.e.78.18%) developed apnea on day 2-7 and this findings is statistically significant. This finding is consistent with observation of some previous studies. Similar observations were found in other studies also [28-31]. 60% of our study population had ≥ 3 apneic episodes. In most other series the apneic neonates suffered from three or more episodes [28,29].

Sepsis and apnea of prematurity has traditionally been described as two commonest etiologies of neonatal apnea. In our study also infection (47.27%) and apnea of prematurity (25.45%) has been shown to be the two commonest causes. Other less important causes were Respiratory distress syndrome (8.18%), hypoglycaemia(5.45%), Anemia(1.81%), seizures, hypocalcemia and PDA. Similar findings were observed by other researchers [28-32].

These findings can be correlated with the statement by Thomas N Hensen et al (2011) that it is imperative that infection should be definitely ruled out or diagnosed and treated in all cases of recurrent apneic episodes. This is an important part of clinical practice with premature infants [32].

Our study revealed that the mean birth weight and gestational age were 1598.36 gm±559.9gm and 32.44 wks±2.39 wks for the infection group and 1094.07gm±189.8 gm and 30.0wks±1.17 wks for the apnea of prematurity group respectively.

These findings corroborate with the observations by other authors [28,33]. In most study-series it is evident that in cases of more mature babies (>32 wks) the underlying cause is sepsis rather than apnea of prematurity. Findings in our study also conform to this concept.

The fact that survival rate in apnea of prematurity group is consistently more favourable than in sepsis group and other etiologies has also been established by our study. Survival rate in neonates of apnea of prematurity group was 71.42% as compared to 42.30% in apnea due to infection group. Similar observations were found in other studies [28,34,35].

Associated problems like intraventricular hemorrhage, bronchopulmonary dysplasia worsen the prognosis and reduce survival rate [34]. Hypocalcemic seizures on the other hand carries an excellent prognosis [35].

Outcome in relation to birth weight was also studied. In our series, percentage of survival in<1000gm,1000-1499gm, 1500-2499 gm and ≥2500 gm was 22.85, 55.5, 66.6 and 100 percent respectively(p<0.001). This finding is consistent with other series except mortality in >1000gm group [36]. The high mortality in >1000gm in our series was possibly due to associated co-morbidities.

In almost all research works on apneic neonates in our country and abroad, survival rate increases, as gestational age increases. In our study percentage of survival in ≤30 weeks, 31-32 weeks, 33-36 weeks and ≥37 weeks were 26.66,51.35,80.0 and 100 percent respectively(p<0.0001). These observations corroborate with findings of other researchers also.[37]

The present study helps us to know the different etiologies of apnea in neonates presenting to a neonatal care unit of a tertiary care Medical College Hospital. Sepsis and apnea of prematurity was found to be the two leading causes of apnea in neonates in our study. Excepting very minimal differences the outcomes in relation to gestational age and birth weight were consistent with the observations by other research works in this field. The differences in findings with respect to these parameters may be due to differences in socio-economic profiles and mostly due to presence of associated comorbidities.

Conclusions

It can be concluded that all babies born at or less than 32 weeks of gestation need to be closely monitored for apnea. Apneic spells occurring at or near term is always abnormal and should be investigated accordingly for exclusion of underlying secondary causes. Sepsis came out to be the commonest cause of apnea and carries uniformly bad prognosis. Apnea of Prematurity which came out to be the second commonest cause on the other hand, does not alter the outcome; if however not associated with other co-morbidities. More and larger studies are needed in this area to substantiate these findings and to look for any newer findings.

Contributions

- Dr Pal drafted the final manuscript and added important intellectual contents. He supervised the study also.
- Dr Jha actually planned and conducted the study. He collected and compiled the data.
- Dr Bandyopadhyay performed statistical analysis. He provided necessary assistance and co operation during the entire study.
- Prof Dr Chakraborti gave necessary guidance during the study. He also added some intellectual contents.
- Prof Dr Mandol provided all sorts of technical guidance and assistance for the work.
- Dr Ali maintained all coordination with the departments of Pathology, Radiology, Biochemistry and Microbiology as and whenever needed.

What was already known in this field?

1. Sepsis and apnea of prematurity are the two leading causes of neonatal apnea.
2. Apnea of prematurity if not associated with other comorbidities bears uniformly good prognosis.
3. Prognosis of apnea of prematurity is good if gestational age is higher and birth weight is higher.

Secondary causes of apnea like sepsis, CNS- insult carries uniformly poor prognosis.

What has been revealed in our study?

1. Sepsis and apnea of prematurity are the two leading causes of neonatal apnea.
2. Apnea of prematurity if not associated with other comorbidities bears uniformly good prognosis.
3. Prognosis of apnea of prematurity is good if gestational age is higher and birth weight is higher; but in our series we observed some neonates with higher birth weight and higher gestational age to have bad outcome (mortality). This may be explained in terms of difference in geographical and social variables and/or associated comorbidities.

Secondary causes of apnea like sepsis, CNS- insult carries uniformly poor prognosis.

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