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Pattern and determinants of newborn apnea in an under-resourced Nigerian setting

TA Ogunlesi, OB Ogunfowora

Department of Paediatrics, Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria

Abstract

Objective: To determine the prevalence, distribution and determinants of newborn apnea in a resource-constrained setting.

Design: Retrospective study.

Materials and Methods: Newborn babies who had apnea during hospitalization between January and December 2008 were studied. The sex, age and body weight, clinical conditions, etiologies of apnea and outcome were recorded. Babies with and without apnea were compared using bivariate and multivariable analysis.

Results: Out of 402 babies seen during the review, 78 (19.4%) had apnea. They comprised 59 preterm and 19 term babies. Forty (51.3%) had apnea at the point of admission while the remaining 38 (48.7) developed apnea after a mean interval of 118.5 ± 101.1 hours. Thirty-seven percent of preterms had idiopathic apnea. Etiologies included respiratory distress (50.0%), hypothermia (42.3%), and asphyxia (28.2%). Multivariate analysis showed that weight <2.5kg, hypothermia, referred status and presence of respiratory distress were determinants of apnea. Case fatality rate was 82.2% among apneic babies.

Conclusion: Apnea occurred commonly in this population of babies. Stringent efforts like ventilator supports for babies in respiratory distress, better perinatal care including thermoregulation are required to reduce the occurrence of the major risk factors for newborn apnea. The identified determinants can be used to draw up effective preventive measures in resource-poor settings.

Key words: Apnea, hypothermia, newborn death, prematurity, respiratory centre

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Introduction

Apnea is defined as the cessation of breath for at least 20 seconds or for lesser period in the presence of bradycardia, cyanosis or other evidences of oxygen desaturation. This condition denotes a state of ineffective control of respiratory activities either as a result of poorly functioning central control mechanisms or from peripheral diseases of the airways.[1] Apnea is a relatively common finding among critically ill babies in Levels II and III neonatal care, world over.[1] This is often ascribed to the relatively immature state of the respiratory centre in the brain of newborn infants which translates to poor adaptation to and response to hypoxic states. Therefore, apnea is also a common manifestation of diseases affecting the brain: infections, hemorrhages, infarction, metabolic derangements and local structural defects.[2]

Apnea is a common cause of newborn morbidity as it has been reported to occur among about 10 percent of hospitalized babies in a Chinese province[3] as well as 25% in Mexico City.[4] A descriptive study of babies who had exchange transfusion for hyperbilirubinemia also reported a prevalence of 12% for apnea.[5] Further, it is also a leading cause of perinatal and neonatal mortality in some poor resource parts of the developing world, where resuscitative measures are sub-optimal.[6,7] Indeed, apnea has been shown

Address for correspondence:
Dr. T. A. Ogunlesi,
P. O. Box 652, Sagamu, Ogun State, Nigeria.
E-mail: tinuade_ogunlesi@yahoo.co.uk

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to predict mortality in the very low birth weight newborn by a factor of three in India.[8]

The clinical diagnosis of newborn apnea has been improved with the use of polysomnography, electrocardiography and pulse oximetry.[9] Indeed, neonatal intensive care facilities in the developed world routinely use mechanical devices to monitor high-risk babies for apnea in order to reduce the risk of Acute Life Threatening Events and Sudden Infant Death syndrome.[1] Unfortunately, such devices are almost nonexistent in most parts of the developing world where newborn death is alarmingly high and a large number of perinatal and neonatal deaths occur from recurrent apnea.[7]

Apnea of prematurity is a separate clinical entity among very preterm infants ascribed to immaturity of the respiratory center in the brain.[1] Thus, preterm infants are most at risk of apnea as a result of immaturity and higher predisposition to infections and metabolic derangements. Expectedly, the burden of apnea is expected to be higher in settings where preterm infants dominate neonatal high-risk admissions and contribute mostly to neonatal mortalities.[10]

Therefore, an epidemiological approach is required to address the problem of newborn apnea in the developing world where all the mechanical devices required for the detection and management of apnea in newborns are almost nonexistent. The ultimate aim will be to identify possible risk factors and devise effective preventive measures. This study was designed to describe the pattern of occurrence and determinants of apnea in an under-resourced neonatal unit to facilitate the generation of appropriate data.

Materials and Methods

The hospital records of babies admitted into the Neonatal Unit of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria, between January and December 2008 were retrospectively studied. The hospital is situated in Sagamu, a semiurban community sandwiched between Lagos, the commercial capital of the country and Ibadan, the largest city in West Africa. It provides specialized care for babies delivered in the maternity unit of the hospital as well as those referred from other public and privately owned health facilities.

All babies admitted in to the unit (except those admitted for observation) are closely monitored for features of cardiorespiratory instability including apnea. For the purpose of this study, apnea is defined as cessation of breath for up to 20 seconds or for less than 20 seconds in the presence of bradycardia or cyanosis. Facilities for polysomnography, electro-oculography, pulse oximetry, electrocardiography, nasal airflow measurement are not available in this unit hence, only skin color, heart rate and chest movement are commonly used to detect apnea in the babies. Apneic babies not responding to brief tactile stimulation are resuscitated with airway clearance, intermittent positive pressure ventilation, intranasal oxygen and cardiac compression as necessary. Babies with periodic breathing (defined as cessation of breath for less than 20 seconds and without bradycardia or cyanosis) were excluded. Gasping babies were also excluded.

Investigations carried out included random blood glucose (RBG), packed cell volume (PCV), serum electrolytes and urea and blood culture. Transfontanelle ultrasound scan and chest X-ray were done as clinically indicated. Preterm infants who are otherwise previously well who developed apnea with normal random blood glucose, hematocrit, serum electrolytes and negative blood culture were diagnosed with idiopathic apnea. Babies with recurrent apnea are managed with intravenous aminophylline 5 mg/kg slowly stat and this is maintained with 2.5 mg/kg 8-12 hourly. Severe anemia (PCV < 30%), hypoglycemia (RBG < 2.2 mmol/l) and significant hypothermia (axillary temperature < 36.5°C)[11] are corrected according to standard protocols. Preterm babies with estimated gestational age (EGA) < 35 weeks and respiratory distress are placed on prophylactic aminophylline as described above. This is continued until the babies have been apnea-free for at least 48 hours.

The data obtained included age on admission, age at the onset of apnea, weight, sex, places and modes of delivery, age at the onset of apnea, number of apneic episodes, clinical disorders, axillary temperature at the onset of apnea and results of PCV and RBG and blood glucose at the onset of apnea. EGA was only estimated among babies who presented within the first 48 hours of life using the modified Ballard scoring system.[12] The other babies (whose EGA could not be ascertained) were classified into term, preterm or post-term using clinical features. The immediate outcome of treatment was recorded as discharge, death or discharge against medical advice. Babies with and without apneawere compared for demographic and clinical features using bivariate methods to identify possible clinical and laboratory features significantly associated with apnea. Variables with significant relationship with apnea were entered into a logistic regression model to identify possible determinants of apnea.

Data were processed with SPSS 15.0 software using descriptive and inferential statistics. Means were compared with Student's 't' test while proportions were compared with odds ratio (OR) and 95% confidence interval (CI). Statistical significance was established when *P*-values were less than 0.05 or 95%CI-excluded unity.

Results

General description of subjects

A total of 402 babies were admitted during the period studied: they comprised 150 (37.3%) in-born and 252 (62.7%) out-born. The out-born babies were delivered in private clinics (112; 27.9%), general hospitals (54; 13.4%), traditional birth homes (29; 7.2%), primary health centers (22; 5.5%), maternity home (16; 4.0%), family homes (11; 2.7%) and spiritual homes (8; 2.0%). There were 225 (56.0%) males and 177 (44.0%) females giving a male-to-female ratio of 1.3:1.

Pattern of apnea

Seventy-eight (19.4%) babies had at least one episode of apnea. These comprised 46 (59.0%) males and 32 (41.0%) females. There were 59 (75.6%) preterm and 19 (24.4%) term babies. The mean age of babies with apnea was 54.5 ± 110.8 hours compared with 56.4 ± 88.7 hours for nonapneic babies (t = 0.16; $P = 0.87$).

The age at the onset of apnea varied from 0.5 to 576 hours with a mean of 111.7 ± 153.6 hours. The distribution of preterm and term babies according to the age at the onset of apnea was similar as shown in Table 1. The mean age of preterm babies at the onset of apnea was 124.6 ± 100.6 hours compared with 71.8 ± 70.4 hours for term babies. The difference was statistically significant (t = 2.12; $P = 0.037$).

Overall, 40 (51.3%) babies had apnea at the point of admission while 38 (48.7%) developed apnea after admission and the interval between admission and occurrence of apnea in the latter group ranged from 5 to 557 hours with a mean of 118.5 ± 101.1 hours. While all the term babies in this study had apnea at the point of admission, 21 (35.6%) and 38 (64.4%) of preterm babies had apnea at the point of admission and after admission, respectively.

Table 2 shows that most of the babies had > 4 episodes of apnea. Most of the babies who had single episodes of apnea were term (55.6%; OR = 0.1, CI = 0.04 – 0.52) while most of the babies with > 4 episodes of apnea (94.1%; OR = 10.1, CI = 1.95 – 29.54) were preterm. These observations were statistically significant.

The prevalence of apnea was highest (86.7%) among babies weighing < 1 kg and progressively declined to 5.8% among babies weighing ≥ 2.5kg as shown in Table 3. Among the 297 babies whose EGA could be determined with certainty, the presence of apnea also progressively declined from 60.5% among babies with EGA < 32 weeks to 7.9% among babies with EGA ≥ 37 weeks as shown in Table 3. In addition, significantly higher proportions of apneic babies weighed < 1 kg while a significantly higher proportion of nonapneic babies weighed ≥ 2.5 kg. Furthermore, a significantly higher proportion of apneic babies had EGA < 32 weeks while a significantly higher proportion of nonapneic baby had EGA ≥ 37 weeks.

Etiologies

Twenty-two (37.3%) of 59 preterm babies had idiopathic apnea. The EGA of these babies with idiopathic apnea ranged from 26 to 33 weeks with a mean of 32 ± 5.9 weeks. Overall, apart from idiopathic apnea (22; 28.2%), other possible etiologies included respiratory distress (from pneumonia, meconium aspiration and probable respiratory distress syndrome) (39; 50.0%), significant hypothermia (33; 42.3%), severe anemia (29; 37.2%), asphyxia (25; 28.2%), hypoglycemia (23; 29.5%), seizures (21; 26.9%), sepsis (15; 19.2%), kernicterus (10; 12.8%) and tetanus (2; 2.6%). Some of the babies had multiple etiologies.

Table 1: Distribution of babies according to the age at the onset of apnea

Age (Hours)	Total	Preterm		Term		Statistics
	N (%)	N	%	N	%	
< 24	32 (41.0)	21	65.6 (35.6)	11	34.4 (57.9)	OR = 0.4 (0.12 – 1.30)
25 – 72	17 (21.8)	14	82.3 (23.7)	3	17.7 (15.8)	OR = 1.6 (0.37 – 8.38)
73 – 168	11 (14.1)	9	81.8 (15.3)	2	18.2 (10.5)	OR = 1.5 (0.26 – 11.42)
> 168	18 (23.1)	15	83.3 (25.4)	3	16.7 (15.8)	OR = 1.8 (0.41 – 9.13)
Total	78 (100.0)	59		19		

KEY: Figures in parentheses are percentages of the respective column

Table 2: Distribution of babies according to the number of apnea

Number of episodes	Total N (%)	Preterm N (%)	Term N (%)	Statistics OR*(CI**)
1	18 (23.1)	8 (13.6)	10 (52.6)	0.1 (0.04 – 0.52)
2 – 4	26 (33.3)	19 (32.2)	7 (36.9)	0.8 (0.24 – 2.75)
> 4	34 (43.6)	32 (54.2)	2 (10.5)	10.1 (1.95 – 29.54)
Total	78	59	19	

KEY: Figures in parentheses are percentages of the total in the respective column

The age of preterm babies at the occurrence of idiopathic apnea ranged from 44.5 to 240 hours with a mean of 53.2 ± 104.1 hour. This mean age was significantly lower than 164.6 ± 173.5 hour (range 1-576 hours) recorded among preterm babies with other etiologies (t = 2.73; *P* = 0.008). Similarly, following the exclusion of all preterm babies with idiopathic apnea, the mean age of babies at the onset of apnea was significantly lower among babies with asphyxia compared with babies with kernicterus (43.6 ± 85.0 hours Vs 103.2 ± 19.7 hours; t = 2.18, *P* = 0.037).

Possible risk factors

Table 4 shows that apnea occurred more frequently among babies who were referred (OR = 5.2), weighed < 2.5kg (OR = 9.5), preterm (OR = 7.6), products of multiple gestation (OR = 2.4) and those who were delivered vaginally (OR = 0.5). Similarly, apnea was significantly more common among babies with significant hypothermia (OR = 5.5), kernicterus (OR = 2.4), seizures (OR = 1.8), respiratory distress (OR = 9.9), severe anemia (OR = 2.4) and hypoglycemia (OR = 2.8). On the other hand, male sex, age on admission ≤ 72 hours or the presence of asphyxia had no significant relationship with occurrence of apnea. Further, apnea occurred among 27.2% (22/81) of babies with positive blood culture compared with 17.5% (11/63) of babies with negative blood culture but the difference was not significant (OR = 1.7; CI = 0.73 – 4.31).

Multivariable analysis of possible risk factors for apnea using logistic regression model is described in Table 5. Weight < 2.5kg (OR = 4.4), referred status (OR = 4.6), significant hypothermia (OR = 6.7) and respiratory distress (OR = 17.3) had significant independent association with apnea. On the other hand, preterm birth, multiple gestation, kernicterus, seizures, severe anemia and hypoglycemia were not independently associated with apnea.

Outcome

The mean duration of admission for apneic babies was 9.5 ± 14.6 days compared with 8.9 ± 6.9 days for nonapneic babies. The difference was not statistically significant (t = 0.53; *P* = 0.594).

Five (6.4%) apneic babies and 32 (9.9%) nonapneic babies were discharged against medical advice and were excluded from the determination of Case Fatality Rates (CFR). The CFR among apneic babies was 82.2% (60/73) compared with

Table 3: Comparison of babies with and without apnea according to body weight and estimated gestational age

Parameters		Total	Apnea present		Apnea absent		OR** (CI***)
			N	%	N	%	
EGA*	< 32 Weeks	51 (17.2)	31	60.8 (49.2)	20	39.2 (8.5)	10.4 (5.02 – 27.56)
	32 – 36 weeks	69 (23.2)	18	26.1 (28.6)	51	73.9 (21.8)	1.4 (0.73 – 2.81)
	> 37 Weeks	177 (59.6)	14	7.9 (22.2)	163	92.1 (69.7)	0.1 (0.06 – 0.25)
Weight	< 1 kg	15 (3.7)	13	86.7 (16.7)	2	13.3 (0.6)	32.2 (6.68 – 21.97)
	1 – 1.49 kg	66 (16.4)	31	46.9 (39.7)	35	53.0 (10.8)	5.4 (2.90 – 10.06)
	1.5 – 2.49 kg	96 (23.9)	21	21.9 (26.9)	75	78.1 (23.2)	1.2 (0.67 – 2.22)
	> 2.5 kg	225 (56.0)	13	5.8 (16.7)	212	94.2 (65.4)	0.1 (0.05 – 0.21)

KEY: Figures in parentheses are percentages of the total in the respective column; *Estimated gestational age; **Odds ratio; ***95%confidence interval

Table 4: Comparison of the prevalence of apnea among different clinical groups of babies

Factors	Total number N = 402	Number with apnea N = 78	Statistics OR*(CI**)
Male sex	225	46 (20.4)	1.1 (0.75, 1.92)
Out-born	252	68 (26.9)	5.2 (2.57, 10.41)
Age < 72 hrs	312	65 (20.8)	1.6 (0.81, 2.98)
Weight < 2.5 kg	177	65 (36.7)	9.5 (5.00, 17.92)
Preterm	153	59 (38.6)	7.6 (4.29, 13.43)
Multiple gestation	81	26 (32.1)	2.4 (1.40, 4.25)
Vaginal delivery	291	64 (22.0)	0.5 (0.21, 0.95)
Hypothermia	134	49 (36.6)	5.5 (3.23, 9.31)
Asphyxia	174	37 (21.3)	0.6 (0.38, 1.03)
Kernicterus	29	10 (34.5)	2.4 (1.05, 5.30)
Seizure	75	21 (28.0)	1.8 (1.03, 3.28)
Respiratory distress	110	53 (48.2)	9.9 (5.70, 17.29)
Severe anemia	92	29 (31.5)	2.4 (1.43, 4.18)
Hypoglycemia	101	33 (32.7)	2.8 (1.63, 4.65)

KEY: Figures in parentheses are percentages; *Odds ratio **95%confidence interval

Table 5: Multivariable analysis of risk factors for apnea using logistic regression

Variables	OR* (CI**)	*P*-values
Weight < 2.5kg	4.4 (1.14, 16.98)	0.03
Preterm birth	2.4 (0.64, 8.66)	0.19
Multiple	1.5 (0.66, 3.62)	0.30
Out-born	4.6 (1.62, 13.21)	0.004
Hypothermia	6.7 (3.23, 14.05)	< 0.0001
Kernicterus	0.3 (0.09, 1.57)	0.18
Seizure	1.8 (0.70, 4.51)	0.22
Respiratory distress	17.3 (7.60, 29.11)	< 0.0001
Severe anemia	1.3 (0.61, 2.86)	0.46
Hypoglycemia	1.4 (0.67, 2.80)	0.38

KEY: *Odd ratio; **95% confidence interval

8.6% (25/292) among nonapneic babies (OR = 49.9). All the apneic term babies died whereas 69.5% (41/59) of the apneic preterm babies died.

Discussion

The prevalence of apnea in the cohort of Nigerian babies studied was 19.4% which literarily translated to apnea occurring in one out of every five hospitalized babies. This undoubtedly confirmed our suspicion that apnea was a common morbidity among high-risk babies and thus, justified this study. The prevalence observed in this study is lower than 25% earlier reported from Mexico City[4] but higher than 9.8% reported from China.[3] The differences might be explained in terms of the overall characteristics of the population studied in each case, particularly in terms of the spectra of the prevalent clinical conditions necessitating the hospitalization of babies. Unfortunately, there is serious dearth of local data on the prevalence of apnea in the West African subregion with which the present findings could be compared. This further justifies the present study as an effort toward generating baseline epidemiological data on apnea.

Most of the babies had apnea on admission and that further suggests the severity of their respective illnesses. This is not surprising since the babies hospitalized in this unit are usually critically ill.

In the same vein, the prevalence of apnea was highest in the first 24 hours of life and among preterm and low birth weight babies. This pattern agrees with previous reports from within[7] and outside[4] Nigeria. This early presentation of apneic cases may reflect the role of perinatal events, particularly birth-related events, in causing apnea. Furthermore, small babies are at higher risk of apnea because of relative immaturity of the brainstem regulatory function[2] on respiration. Furthermore, babies who require hospitalization within the first 24 hours of life should be closely monitored for the risk factors for apnea and these factors, if present, should be aggressively treated.

In a study of neonatal deaths at this centre, apnea caused deaths mostly among babies weighing < 1500 g and very few of babies weighing between 1500 and 2499 g but none of babies weighing > 2500 g.[7] However, apnea occurred among all weight groups in the present study. Interestingly, the prevalence was highest among babies weighing <1000 g and babies with EGA < 32 weeks in agreement with previous reports.[3]

Nevertheless, idiopathic apnea, being a diagnosis of exclusion was so diagnosed from the absence of most of the common clinical disorders which ordinarily would cause apnea in this population of clinically preterm infants. In addition, high noise level in the neonatal intensive care unit had been shown to create excessive auditory stimulation which provokes negative physiological events like apnea.[13] This may be responsible for some cases of unexplained apnea especially among preterm babies. It is important to take this into consideration when making diagnosis of idiopathic apnea.

The significant role of outside delivery as a risk factor for apnea in this study concurs with previous findings that babies delivered outside the hospital are at higher risk of morbidities and mortalities[14] Respiratory distress may be closely related to the occurrence of apnea in the newborn[1] and this may reflect the role of poor adaptation to hypoxic conditions and possible alteration of the chemical control mechanisms in respiration. It is very likely that early commencement of respiratory supports may prevent the occurrence of apnea when babies have respiratory distress. This is hinged on early detection of oxygen desaturation. To this end, facilities for pulse oximetry should be made available for routine use in centers caring for critically ill babies. The role of hypothermia and hypoglycemia in apnea had earlier been described.[15] Unfortunately, both hypothermia and hypoglycemia are closely related and tend to coexist.[16] Therefore, babies with, or at risk of either hypothermia or hypoglycemia should be aggressively managed and closely monitored to prevent apneic episodes. Although, kernicterus did not have a significant independent association with apnea in the present study, it is an important but highly preventable cause of apnea.[17] The exact pathogenesis is still unclear but studies have demonstrated possible damage to brainstem respiratory centers during the deposition of bilirubin in the brain.[17]

It is remarkable that more than three-quarter of apneic babies died. Surprisingly, all apneic term babies died whereas about two-thirds of apneic preterm babies died. This may be related to the preponderance of idiopathic apnea among preterm babies since this condition often resolves with increasing maturity and postconceptional age. On the other hand, the term babies most likely had definite pathologies and this may explain their higher CFR.

The retrospective nature of the present study is acknowledged as a limitation. In addition, the lack of appropriate diagnostic facilities limited the investigation of apneic babies as well as prevented the classification of apnea into central, obstructive or mixed.

In conclusion, apnea was a common morbidity and cause of mortality in this Nigerian newborn unit. Fortunately, most of the predisposing factors and statistically derived determinants can be adequately prevented with quality obstetric and perinatal care services. Therefore, effective preventive measures can be developed using the findings in the present study. Furthermore, efficient screening tools can be designed using the significant determinants in order to facilitate early detection and prompt management of babies at risk of apnea in other resource-poor settings in the world.

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