Clinical audit on management of apnea of prematurity in neonatal intensive care unit

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Introduction
Apnea of prematurity (AOP) is one of the most common diagnoses in the neonatal intensive care unit (NICU). An apneic spell is usually defined as a cessation of breathing for 20 s or longer or a shorter pause accompanied by bradycardia, cyanosis, or pallor. The incidence of AOP increased with decreasing gestational age. Essentially, all infants born at less than or equal to 28 weeks of gestation were diagnosed with apnea. Apnea may be obstructive, central, or mixed. Idiopathic AOP is mostly of mixed etiology (50–75). The physiopathological mechanism underlying AOP is not fully clear, but is certainly linked to the immaturity of the central nervous system of the preterm neonate. Apnea is a diagnosis of exclusion. It usually resolves by 36–37 weeks' corrected age without long-term sequelae.

Patients and methods
The study includes all preterms at NICU in Assiut University Children Hospital with idiopathic apnea of prematurity in a period of 1 year (March 2018–March 2019). The study included 50 preterm neonates admitted to the NICU with idiopathic AOP. Their ages ranged from 27 to 34 weeks, 27 male and 23 female. The study is a clinical audit to detect the adherence of physicians to the Protocol for Management of AOP at NICU in Assiut University Children Hospital.

Results
A total of 54% were males whereas 46% were females. Gestational age of the studied cases range from 27 to 34 weeks with a mean age of 30.4 ± 1.99 weeks. Caffeine citrate treatment was given in 100% of the studied cases; 68% of them showed good response to caffeine citrate therapy. A total of 86% of the studied cases improved and discharged without further attacks of apnea; 14% of the studied cases died during the study due to complications and sequela of the disease.

Conclusion
Stark's 2016 Guidelines have been followed in the management of idiopathic pnea of prematurity in the studied cases but there were some defects that can affect the outcome of management of idiopathic apnea of prematurity. The study recommends avoiding these defects.

Keywords:
apnea of prematurity, caffeine citrate, pediatric, preterm

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Introduction

Apnea of prematurity (AOP) is one of the most common diagnoses in neonatal intensive care unit (NICU) [1–6]. Each year 15 million infants are born premature (<37 weeks' gestation) worldwide, and that the number is on the rise [7]. Apnea is a developmental disorder that frequently affects preterm infants, especially those of lower gestational age (GA). It is partly due to the physiological immaturity of the central nervous system, in particular poor myelination of the immature brainstem, and for that reason it spontaneously improves as GA increases [8].

Apnea is usually defined as a cessation of breathing for 20 s or longer or a shorter pause accompanied by bradycardia (<100 beats/min), cyanosis, or pallor [2]. The incidence of AOP increased with decreasing GA [3].

Apneic episodes in preterm infants may be central (absent inspiratory efforts), obstructive (airway obstruction with present inspiratory efforts), or mixed (combination of central and obstructive mechanisms), with latter being the most common form [9].

AOP is a diagnosis of exclusion and, therefore, a thorough evaluation for secondary causes such as sepsis of the newborn, necrotizing enterocolitis, intraventricular hemorrhage, etc., should be performed depending on the clinical presentation [6].

The management of AOP starts with eliminating the factors that increase the risk of apnea such as maintenance of a stable thermal environment, nasal patency, and avoidance of extreme neck flexion and extension. In preterm infants with obstructive or mixed apnea, nasal continuous positive airway pressure (CPAP) or oxygen/air flow through a nasal cannula may help to decrease the frequency and severity of episodes. Methyl xanthine therapy especially with caffeine has been shown to be effective in the treatment of symptomatic preterm infants with AOP [9].

AOP does not alter an infant's prognosis unless it is severe, recurrent, and refractory to therapy.

AOP usually resolves by 37 weeks of postconceptional age, although it may persist beyond term gestation, particularly in extremely preterm infants born at less than 28 weeks of gestation, and does not predict future episodes of sudden infant death syndrome [4].

Aim

Clinical audit conducted to detect the adherence of physicians to the Protocol for Management of AOP at NICU in Assiut University Children Hospital.

Patients and methods

The study included 50 preterm neonates admitted to the NICU with idiopathic AOP over 1 year from March 2018 to March 2019. Their ages ranged from 27 to 34 weeks; there were 27 men and 23 women. Informed consent was taken in a written format from parents. Ethics committee, Assiut Faculty of Medicine approved the study.

Inclusion criteria

(1) Preterm neonates with idiopathic AOP.

Exclusion criteria

(1) Other causes of apnea in preterm neonates.
Exclusion is mainly by investigations:
   (a) Septic screen (complete blood count, C-reactive protein, and blood culture) to exclude septic causes
   (b) Arterial blood gases and serum electrolytes to exclude metabolic causes
   (c) Random blood sugar to exclude hypoglycemia
   (d) Imaging study (not done to all cases but only when clinical data suspects specific disorder) such as chest radiography to exclude respiratory causes, abdominal radiography, and sonography to exclude necrotizing enterocolitis, echocardiography to exclude congenital cardiac problems, cranial ultrasound or computed tomography (CT) to exclude neurological insult.

(2) Full-term neonates.

Tools of the study

An observational checklist based on Stark's 2016 Guidelines for the management of AOP [10] developed by the investigators in order to assess the management of patients with AOP.

The parameters to be assessed

Cardiorespiratory monitoring, investigation for the diagnosis of idiopathic AOP, and management protocols.

Results

The study included 50 preterm neonates admitted at NICU in Assiut University Children Hospital with idiopathic AOP during a period of 1 year.

Discussion

AOP is one of the most common diagnoses in NICUs [1]. Each year 15 million infants are born premature (<37 weeks' gestation) worldwide, and that the number is on the rise [7]. Apnea is inversely related to GA. The lower the GA, the higher the incidence of apnea [3]. The study was conducted on all preterm neonates admitted at NICU in Assiut University Children Hospital with idiopathic AOP during a period of 1 year. The study was concerned with assessment of the degree of adherence of physicians to the protocol for the management of AOP at NICU in Assiut University Children Hospital according to the guidelines [10].

As regards demographic data of the studied cases as shown in Table 1, the study included 50 preterm neonates, 54% males and 46% females. Most of the studied cases (80%) were delivered via cesarean section and 20% though normal vaginal labor. The GA of the studied cases range from 27 to 34 weeks with mean GA of 30.4 ± 1.99 and an average mean birth weight of 1.2 ± 0.3 kg. This may explain the high incidence of apnea among preterm and extreme low birth weight neonates.

AOP is a diagnosis of exclusion, therefore history, examination, and a full-through evaluation is needed to exclude the secondary causes of apnea and confirm

Table 1 Sociodemographic characteristics of patients

Parameters	Range (mean±SD) or *n* (%)
Sex	
Male	27 (54)
Female	23 (46)
Gestational age (weeks)	27-34 (30.42±1.99)
Birth weight (kg)	0.8-1.9 (1.23±0.3)
Mode of delivery	
CS	40 (80)
NVD	10 (20)

CS, cesarean section; NVD, natural vaginal delivery.

Table 2 Recorded data regarding the diagnosis of idiopathic apnea of prematurity

Parameters	Recorded (done) [*n* (%)]	Not recorded (not done) [*n* (%)]
History		
Prenatal		
Parity	50 (100)	0
Maternal disease	30 (60)	20 (40)
Maternal medication	32 (64)	18 (36)
Natal (birth)		
Type of delivery	50 (100)	0
Obstructed labor	50 (100)	0
Medication or anesthesia before delivery	50 (100)	0
Postnatal symptoms		
Crying	50 (100)	0
Cyanosis	50 (100)	0
Convulsion	40 (80)	10 (20)
Jaundice	15 (30)	35 (70)
Examination		
General examination	50 (100)	0
Chest examination	50 (100)	0
Heart examination	50 (100)	0
Abdominal examination	50 (100)	0
Neurological examination	50 (100)	0
Duration of apnea	38 (76)	12 (24)
Record occurrence of apneic attack	50 (100)	0
Cardiorespiratory monitoring		
Heart rate	50 (100)	0
Respiratory rate	50 (100)	0
Blood pressure	50 (100)	0
Oxygen saturation	50 (100)	0

idiopathic AOP [10,11]. According to these data, all studied cases were subjected to full evaluation as demonstrated in Tables 2–4.

Prenatal history including analysis of parity was recorded in 100% of the studied cases; analysis of maternal diseases was recorded in 60% of cases only and analysis of maternal medications were recorded in 64% of studied cases as illustrated in Table 2.

Natal history including the type of delivery, history of obstructed labor, and history of medication or anesthesia before delivery were recorded in 100% of cases as illustrated in Table 2.

Table 3 Recorded data regarding laboratory evaluation of apnea of prematurity

Parameters	Done [*n* (%)]	Not done [*n* (%)]
Complete blood count	50 (100)	0
C-reactive protein	23 (46)	27 (54)
Blood culture	14 (28)	36 (72)
Arterial blood gases	50 (100)	0
Random blood sugar	49 (98)	1 (2)
Serum electrolytes		
Sodium	34 (68)	16 (32)
Potassium	34 (68)	16 (32)
Calcium	46 (92)	4 (8)

Table 4 Recorded data regarding radiological evaluation of apnea of prematurity

Parameters	Done [*n* (%)]	Not done [*n* (%)]
Chest radiography: indicated in 50 cases	50 (100)	0
Transcranial ultrasound: indicated in 41 cases	41 (100)	0
Echocardiography: indicated in eight cases	8 (100)	0
Abdominal ultrasound: indicated in 10 cases	10 (100)	0
Brain CT: indicated in 0 cases	0	50 (100)

CT, computed tomography.

Postnatal history including history of spontaneous crying and cyanosis after birth was recorded in 100% of cases; history of convulsions were recorded in 80% of cases, and not recorded in 20% of cases; and a history of jaundice was recorded in 30% of cases only and not recorded in 70% of cases as illustrated in Table 2.

Examination of patients in the study including general examination, chest examination, heart examination, abdominal examination, and neurological examination were recorded in 100% of cases.

Assessment of apneic episodes was recorded in 100% of cases and the duration of apneic attack was recorded in 76% of cases and not recorded in 24% of cases. It was shown that 50% of cases manifest once an apneic attack and 50% show repeated episodes of apnea as illustrated in Table 2.

Cardiorespiratory monitoring including assessment of heart rate, respiratory rate, blood pressure, and oxygen saturation to detect any episode of apnea, bradycardia, and desaturation was recorded in 100% of cases as illustrated in Table 2.

All studied cases were subjected to laboratory and radiological evaluation to exclude the secondary causes of apnea and to confirm the idiopathic types.

(1) Laboratory evaluation including:
    (a) Septic screen (to exclude septic causes) through complete blood count was done in

100% of studied cases; C-reactive protein was done in 46% of cases; and blood culture in 28% of cases
   (b) ABGs (to exclude respiratory or metabolic causes). ABG was done in 100% of studied cases
   (c) Random blood sugar was done in 98% of cases
   (d) Serum electrolytes (to exclude electrolyte disturbance); serum sodium and potassium were done in 68% of studied cases; and serum calcium was done in 92% of cases.

   All previous data are illustrated in Table 3.
(2) Radiological evaluation (not done to all cases, recommended when clinical data suggest a specific disorder):
   (a) Chest radiography (to exclude respiratory causes) was done in 100% of clinically indicated cases (50 cases)
   (b) Transcranial ultrasound (to exclude neurological insult such as intraventricular hemorrhage or hydrocephalus) was done in 100% of clinically indicated cases (41 cases)
   (c) CT scan: None of the studied cases were clinically indicated for brain CT scan
   (d) Echocardiography (to exclude congenital heart diseases) was done in 100% of clinically indicated cases which represent eight cases
   (e) Abdominal ultrasound was done in 100% of indicated cases which represent 10 cases.

All previous data are illustrated in Table 4.

Treatment of idiopathic AOP was divided in this study into two main categories, nonpharmacological and pharmacological.

(1) Nonpharmacological treatment of idiopathic AOP among the studied cases includes:
   (a) Resuscitation through tactile stimulation was done properly in 100% of cases
   (b) Positioning of the patients that was done properly in 70% of cases and done improperly in 10% of cases, whereas 20% of the studied cases does not receive concern about proper positioning at all as illustrated in Table 5
   (c) Ensuring thermal stability of the patients was done properly in 70% of cases (neither of them receive improper assessment) and not done in 30% of cases may be due to inattention of physicians about the importance of temperature regulation and its deleterious effects on causing apnea as illustrated in Table 5
   (d) Avoiding oral feeding was done properly in 78% of studied cases. Oral feeding was not avoided in 22% of cases that may be due to low frequent apneic attacks, stable general condition, weight, and GA that favor start of oral feeding among those cases as illustrated in Table 5
   (e) As regards oxygen support to the studied cases:
      (i) Oxygenation via nasal cannula was done properly in 40% of cases and done improperly in 12% of cases; 48% of cases not receive nasal oxygenation as they need more advanced respiratory support either through CPAP or mechanical ventilation as illustrated in Table 5.
      (ii) Ambu ventilation (bag and mask ventilation) was done properly in 100% of clinically indicated cases which represented seven cases only as illustrated in Table 5
   (f) As regards assisted ventilation among the studied cases:
      (i) CPAP was indicated in 100% of the studied cases on the basis of Stark's 2016 Guidelines that recommend the use of CPAP in infants of less than 32 – 34 weeks' GA [10]. As regards these data, CPAP was done properly in 28% of indicated cases which manifest frequent attacks of apnea and done improperly in 6% of indicated cases
      (ii) CPAP was not done in 66% of cases in spite of being clinically indicated and this was due to unavailability of resources, technical errors, and lack of experience of importance of CPAP in apnea among residents. These previous data are illustrated in

Table 5 Recorded data regarding non-pharmacological treatment

Parameters	Done [*n* (%)]		Not done [*n* (%)]
	Properly	Improperly	
Resuscitation			
Tactile stimulation	50 (100)	0	0
Positioning	35 (70)	5 (10)	10 (20)
Thermal stability	35 (70)	0	15 (30)
Avoid oral feeding	39 (78)	0	11 (22)
Oxygenation			
Nasal cannula oxygen	20 (40)	6 (12)	24 (48)
Ambu ventilation (indicated in seven cases)	7 (100)	0	0
Assisted ventilation			
CPAP			
Indicated in 50 cases	14 (28)	3 (6)	33 (66)
Mechanical ventilation			
Indicated in seven cases	7 (100)	0	0
Blood transfusion			
Indicated in 20 cases	0	20 (100)	0

CPAP, continuous positive airway pressure.

Table 5 and Fig. 1

(iii) As regards mechanical ventilation; 100% of clinically indicated cases (only seven cases that manifested severe apneic attacks failed to respond to other lines of treatment) were connected properly to MV as illustrated in Table 5 and Fig. 1

(g) As regards blood transfusion, 100% of clinically indicated cases (20 cases) were given blood transfusion therapy; none of them received transfusion therapy properly (as shown in Table 5) as the transfusion therapy was based mainly on low hemoglobin level and not on hematocrit level which has been approved in recent studies as a reliable marker, more than the hemoglobin level as regards Stark's 2016 Guidelines that consider a transfusion of packed red blood cells, if the hematocrit is less than 25% [10]. These data are illustrated in Table 5.

(2) Pharmacological treatment among studied case includes:

(a) Caffeine citrate treatment was given in 100% of studied cases. A loading dose of 20 mg/kg of caffeine citrate for 1 day was given properly to 100% of the studied cases, followed by a maintenance dose of 5 mg/kg in one daily dose beginning 24 h after the loading dose also given properly in 100% of studied cases. Day of start of caffeine citrate was begun properly in the first day in 100% of cases. These data are discussed in Table 6 and Fig. 2

(b) Duration of caffeine therapy was calculated properly in 60% of cases and improperly in 40% of cases (caffeine treatment was discontinued before 34 weeks, postconceptional age). This disagrees with Stark's 2016 Guidelines that recommend discontinuation of caffeine at 34–36 weeks' postmenstrual age if no apneic spells have occurred for 5–7 days. Duration of treatment ranges between 5 and 28 days with a mean day of therapy of about 12.4 ± 5.52 day. These previous data are discussed in Table 6 and Fig. 2.

All patients in the study that showed response and improvement on caffeine citrate treatment were subjected to a follow-up study for a period of 5 days after stoppage of caffeine citrate treatment to detect any episode of recurrent apneic attack prior to discharge. Follow-up after caffeine stoppage was done among 43 (86%) cases and not done in seven (14%) cases as they die from a sequela of the disease and due to development of complications. Among those infants who improved and undergo follow-up study, 34 (79.1%) cases did not show any further attacks of apnea and nine (20.9%) cases manifested recurrent apneic attacks. All patients were advised for follow-up after discharge (100% of cases) as illustrated in Table 7.

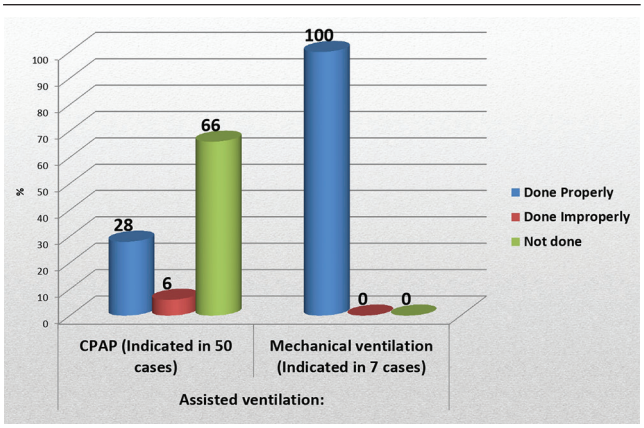
Table 6 Recorded data regarding pharmacological treatment (caffeine citrate treatment)

Parameters	Done [*n* (%)]		Not done [*n* (%)]
	Properly	Improperly	
Loading (20 mg/kg)	50 (100)	0	0
Maintenance (5 mg/kg)	50 (100)	0	0
Day of start (first day)	50 (100)	0	0
Duration (day)	30 (60)	20 (40)	0
Range (days of drug therapy)		5-28	
Mean±SD		12.4±5.52	

Table 7 Recorded data regarding follow-up after caffeine citrate treatment stoppage

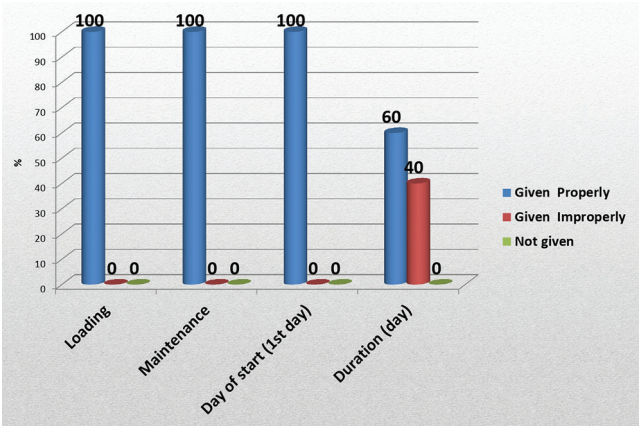
Parameters	Done [*n* (%)]	Not done [*n* (%)]
Follow-up	43 (86)	7 (died) (14)
Record recurrent apnea	9 (20.9)	34 (79.1)
Advised for follow-up after discharge	43 (100)	0

Figure 1



Recorded data as regards assisted ventilation.

Figure 2



Recorded data as regards caffeine citrate treatment.

Table 8 Recorded data regarding outcome of apnea of prematurity

Outcomes	Yes [*n* (%)]	No [*n* (%)]
Improved and discharged	43 (86)	7 (14)
Complicated cases	16 (32)	34 (68)
With intraventricular hemorrhage, then improved and discharged	9 (18)	
With neonatal sepsis (fulminant pneumonia) and died	7 (14)	

The outcome of the studied cases show that 86% of the cases improved and discharged without further attacks of apnea (68% of those cases did not show complications or recurrent apneic attacks and 18% develop complications in the form of intraventricular hemorrhage and recurrent apnea but improved later on and discharged without apnea). While 14% of the studied cases were not improved and died during the study due to complications (neonatal sepsis, fulminant pneumonia) and sequela of the disease. These previous data are illustrated in Table 8.

Conclusion

As regards this initial audit about the management of AOP at the NICU in Assiut University Children Hospital, we concluded that there is no complete adherence to Stark's 2016 Guidelines. Our study demonstrated lack of compliance to the protocol of management of apnea, as regards the analytic aspects of diagnosis. Also, there is no complete adherence to the nonpharmacological aspects of therapy. On the other hand, pharmacological aspects of therapy seemed to be implemented properly which were reflected in our study outcome.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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