Research and Reports in Neonatology

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REVIEW

Apnea of prematurity: challenges and solutions

This article was published in the following Dove Press journal:
Research and Reports in Neonatology
19 June 2014
Number of times this article has been viewed

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Abstract: Apnea of prematurity is a developmental disorder that frequently affects preterm infants, especially those with lower gestational age. Even if apnea of prematurity is by definition a self-limiting condition, it can cause serious problems during the hospital stay and can potentially have long-term neurological and cognitive consequences depending on the severity and intensity of the episodes. The diagnosis of apnea of prematurity can be made only after excluding a number of diseases of the preterm infant in which apnea may be an epiphenomenon. Etiological diagnosis is essential for selection of appropriate treatment, which may be nonpharmacological or involve use of drugs.

Keywords: apnea of prematurity, idiopathic and secondary apnea, caffeine

Introduction

Apnea of prematurity (AOP) is a developmental disorder that frequently affects preterm infants, especially those of lower gestational age (GA). AOP 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.[1,2] Even if it has not yet been demonstrated to what extent AOP may affect the neurodevelopmental outcome in preterm infants, it is clear that relevant to the latter is not the effect of apnea per se, but its effects on oxygenation and/or heart rate.[3]

AOP has been defined has cessation of breathing for over 15–20 seconds if accompanied by oxygen desaturation (oxygen saturation ≤80% for ≥4 seconds) and/or bradycardia (heart rate less than two thirds of the basic heart rate for ≥4 seconds) in infants with a GA below 37 weeks.[1]

The incidence of AOP is inversely correlated with GA and birth weight. AOP affects 7% of infants with GA 34–35 weeks, 15% of infants with GA 32–33 weeks, 54% of infants with GA 30–31 weeks, and nearly 100% of infants with GA less than 29 weeks or birth weight less than 1,000 g.[4,5]

Pathophysiology

Apnea is traditionally classified as central (10%–25% of cases), obstructive (10%–25%), or mixed (50%–75%).[6] In central apnea, airflow ceases in the absence of respiratory effort. In obstructive apnea, there is no airflow, even if the infant attempts to breathe throughout the pause; the obstruction seems to be due to a combination of passive pharyngeal collapse and either active or passive laryngeal closure.[7] During mixed apnea, there is first a central apneic phase, followed by an upper airway

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obstruction that worsens the desaturation and bradycardia;[7,8] however, in some cases, airway obstruction can also occur first.[9] Therefore, considering a reciprocal interaction between central apnea and upper airway obstruction, the distinction between purely "central" or purely "obstructive" apneas appears to be mainly theoretical.

Control of breathing and responses to hypercapnia and hypoxia

Control of breathing is maintained by a network of neurons on the ventral medullary surface of the brainstem that receives efferent inputs from central and peripheral chemoreceptors and mechanoreceptors and operates as a negative feedback system. Reflexes such as the laryngeal chemoreflex and the lung inflation (Hering–Breuer) reflex are also involved in the control of breathing, and the brain further controls the basic respiratory pattern.[10,11]

The breathing pattern of a preterm infant, with the presence of periodic breathing, paradoxical ventilation, and immature responses to hypercapnia and hypoxia, resembles that present during fetal life. Fetal respiratory efforts do not influence arterial oxygen and carbon dioxide, so the fetal response to hypoxia is mainly aimed at reducing the consumption of oxygen, resulting in a reduction in respiratory activity.[12,13] Further, carotid body chemoceptors, after the marked increase in arterial oxygen that occurs after birth, have a very low sensitivity in response to hypoxia until they are reset from the fetal to the adult range.[14]

Thus, the preterm infant has a very particular respiratory response pattern to hypercapnia and hypoxia. In response to hypercapnia, a preterm infant, unlike an adult, does not increase respiratory frequency or tidal volume, but lengthens the expiratory period, resulting in a lower volume per minute. This response is increased in infants with AOP.[15] Response to hypoxemia instead is characterized by an initial increase in ventilation for 1–2 minutes, and then the respiratory frequency falls below the starting level. The cause of this depressive phase is not well understood, but this type of response can persist for various weeks of post-natal life.[16] Various neurotransmitters are involved in the hypoxic depressive response, including adenosine, endorphins, and gamma-aminobutyric acid. Neurotransmitter blockers (methylxanthines for adenosine, naloxone for endorphins) act before the late depressive ventilation phase.[17]

Hypoventilation and the low expiratory volumes of preterm infants, which fall further during apnea, seem to be the cause of the early hypoxemia seen during an apneic episode.[3] The associated bradycardia is primarily caused by hypoxemia via stimulation of peripheral chemoreceptors,[15] then potentiated by lack of the lung inflation reflex (that increases heart rate) during the apneic episode.[18] This explains why bradycardia is more common in central apnea than in obstructive or mixed apnea.[6]

Diaphragmatic fatigue

Chest wall distortion, typical of preterm infants, increases the volume displacement of the diaphragm during inspiration, resulting in an increased workload and contributing to the development of diaphragmatic fatigue and apnea.[19]

Feeding and apnea

Apneic episodes are more frequent during feeds, due to immaturity of coordination between breathing, sucking, and swallowing, stimulation of the laryngeal reflex, and diaphragmatic fatigue.[20] Reduced lung volumes due to abdominal distension and increased work of breathing are also associated with an increase in apneic spells after feeds.[21]

Behavioral states and apnea

Apnea spells appear to be more frequent during rapid eye movement sleep which accounts for the largest proportion of sleep time in preterm infants.[22] Arousal from rapid eye movement sleep has also been linked to apnea, via a mechanism related to laryngeal closure and hypoxia.[23]

Genetic basis of AOP

Starting from the observation that the prevalence of AOP was higher among first-degree relatives,[24] recent studies have hypothesized the presence of a genetic susceptibility to AOP. A higher concordance to AOP between monozygotic twins (87% versus 62% for dizygotic twins of the same sex) was found by a study conducted in 317 pairs of premature twins of GA less than 36 weeks, indicating a genetic susceptibility to AOP between twins of the same sex, especially males.[25]

A recent study showed that certain single nucleotide polymorphisms of genes encoding for adenosine receptors A1 and 2A are associated with the highest risk of developing apnea, probably due to increased expression of adenosine receptors. Polymorphisms of genes for A1 and A2A can also contribute to the individual diversity of response to caffeine.[26]

Diagnosis

Diagnosis of AOP is a diagnosis of exclusion, because apnea in preterm infants can be idiopathic or an epiphenomenon of other diseases of prematurity. The most common causes of

Table 1 Causes of secondary apnea in preterm infants

Infections	• Bacterial sepsis (early-onset, late-onset) • Meningitis • Local infections (eg, urinary tract infections) • Invasive fungal infections • Viral infections (eg, respiratory syncytial virus infections)
Respiratory	• Congenital malformations of the upper airways (eg, Pierre–Robin sequence) • Nasal obstruction • Vocal cord paralysis • Tracheal occlusion due to excessive cervical flexion • Respiratory distress • Pneumothorax • Hypoxemia • Hypercarbia • Bronchopulmonary dysplasia
Cardiovascular	• Significant patent ductus arteriosus • Congenital cyanotic heart disease • Congestive heart failure • Increased vagal tone • Severe hypovolemia • Hypotension, hypertension
Neurological	• Hypoxic-ischemic encephalopathy • Intraventricular hemorrhage • Intracranial hemorrhage • Conditions causing increased intracranial pressure • Congenital myopathies or neuropathies • Congenital central hypoventilation syndrome • Central nervous system malformations (eg, Arnold–Chiari malformation, Dandy–Walker syndrome) • Seizures • Pain
Metabolic	• Congenital metabolic disorders (eg, hypothyroidism) • Acidosis • Hypoglycemia • Hypocalcemia • Hyponatremia, hypernatremia • Hypermagnesemia • Hypothermia, hyperthermia
Gastrointestinal	• Necrotizing enterocolitis • Gastroesophageal reflux • Abdominal distension (reduces lung volume and increases vagal stimulation)
Hematological	• Severe anemia

secondary apnea are listed in Table 1. The onset of AOP usually occurs in the first 2 days of life and at the latest by 7 days of life: however, it is not common beyond the first week.

Even if the definition of AOP is widely accepted, the monitoring of intensity and severity of apnea may be quite arbitrary, depending on the limits of alarms, the averaging times, and the subjective choice of the averaging times for the various GAs. This technical heterogeneity may lead to different treatment decisions.

Conditions related to AOP

Other conditions common in preterm infants have been related to AOP, but it is sometimes difficult to understand their relationship.

Anemia of prematurity and AOP

Anemia of prematurity, due to lower tissue oxygenation and the paradoxical response to hypoxia of preterm infants, has been indicated as a factor involved in the pathophysiology of AOP.[27]

Gastroesophageal reflux and apnea

Gastroesophageal reflux and apnea are both common in preterm infants, but their relationship is controversial. Apnea and gastroesophageal reflux, although coexisting in the same infant, are often events separated in time.[28] Acid stimulation of laryngeal chemoreceptors induces a reflex that protects the airway from aspiration, ie, rapid swallowing, apnea, laryngeal constriction, bradycardia, and hypertension.[29] On the other hand, it has also been hypothesized that apnea and associated hypoxemia may reduce tone in the lower esophageal sphincter, predisposing to reflux.[30,31] Even excessive secretions in the upper airway can induce central apnea.

Nonacid refluxes, ie, those that appear immediately after a meal, could trigger apnea via a mechanism linked to distension of the middle esophagus. Acid refluxes, instead, appear mostly in the post-prandial period, when the stomach is partially empty. If they reach the larynx, they could trigger a laryngeal reflex that determines the apnea. There is little evidence that drug therapy for gastroesophageal reflux has positive effects on AOP. Thus, use of antireflux drugs is not justified for the treatment of apneas, although a subgroup of preterm infants with eating disorders seems to benefit from such therapy.[32] Also, thickened formulas do not seem to reduce acid or nonacid gastroesophageal reflux in preterm infants more than non-thickened formulas.[33]

Sudden infant death syndrome and AOP

Sudden infant death syndrome (SIDS) refers to the death of an infant younger than one year of age when this occurs during sleep and remains unexplained despite complete autopsy, examination of the death scene, and review of the clinical history.[34] In the past, studies have shown that there is a causal relationship between SIDS and AOP.[35] The average age for SIDS is around 46 weeks post menstrual age (PMA) for infants born at 24–28 weeks GA and at 52 weeks PMA for those born at term. AOP usually resolves at PMA that precedes the average ages of SIDS occurence. Apnea of

longer duration, which affects most premature infants, generally extends up to a maximum of 43 weeks PMA. AOP is not predictive of SIDS, and a history of AOP does not require the use of a home apnea monitor.[36,37] However, home cardiorespiratory monitoring may be warranted for premature infants who are at high risk of recurrent episodes of apnea, bradycardia, and hypoxemia from hospital discharge until approximately 43 weeks PMA or until cessation of extreme episodes.[37]

Treatment

Resolution of an apneic episode may be spontaneous or may require intervention, ranging from tactile stimulation to resuscitation with oxygen and intermittent positive-pressure ventilation, depending on the degree and duration of hypoxemia and the associated bradycardia. The modes of action for the treatments proposed for AOP are summarized in Table 2.

Nonpharmacological treatment

Posture

Due to the hypotonia present in the neck muscles of neonates, it is very important to avoid both hyperextension and hyperflexion of the neck, which can trigger obstructive apnea. In the prone position (face down), the chest wall is stable and thoracoabdominal asynchrony is reduced; in neonates with respiratory distress, the prone position increases ventilation, reduces the incidence of gastric reflux, and decreases the apnea rate.[38,39] Moreover, an elevated position of 15 degrees reduces the number of hypoxemic events.[40]

It is important to remember that use of the prone position, being associated with an increased incidence of SIDS, can only be considered for infants in neonatal intensive care during cardiopulmonary monitoring, whereas the supine sleeping position (face up) should be recommended in the normal newborn nursery and to all parents at discharge.[37]

Table 2 Mechanism of action of proposed interventions for the treatment of apnea of prematurity

Mechanism of action	Treatment
Reduction of work of breathing	• Prone, head elevated position • nCPAP or nIPPV/nSIPPV
Increased respiratory drive	• Oxygen administration • Red blood cell transfusion (increases tissue oxygenation) • Caffeine • Doxapram (not a standard treatment due to side effects)
Increased diaphragm contractility	• Caffeine • Branched-chain amino acids (there is still a lack of evidence)

Abbreviations: nCPAP, nasal continuous positive airway pressure; nIPPV, nasal intermittent positive pressure ventilation; nSIPPV, nasal flow-synchronized intermittent positive pressure ventilation.

Noninvasive ventilation support

Nasal continuous positive airway pressure (nCPAP) seems to be effective in improving AOP because of several modes of action: it prevents obstruction of the upper airway by splinting the pharynx; it reduces the work of breathing; it stabilizes the rib cage and thus reduces neuronal inhibitory signals to the respiratory center; and it prevents hypoventilation by improving functional residual capacity and expansion of the alveoli.[41]

It is not clear as yet if nasal intermittent positive pressure ventilation and nasal flow-synchronized intermittent positive pressure ventilation (nSIPPV), generally used with a peak inspiratory pressure of 15–20 cm H_2O and a positive end-expiratory pressure of 5–6 cm H_2O, is more effective then nCPAP in treating AOP. However, reductions in apneic episodes and mechanical ventilation requirements due to AOP along with a need for lower caffeine doses have been seen with nSIPPV.[42–44]

High flow nasal cannula

A high flow nasal cannula has been suggested recently as an alternative to other noninvasive forms of ventilatory support because it is often better tolerated by infants. High flow nasal cannula devices can deliver a mixture of heated, humidified, and blended oxygen and air via a nasal cannula at variable flow rates. Due to the potential for delivery of a positive, continuous, distending pressure and to keep the upper airway open, its use has been suggested, with the same rationale of nCPAP, for management of AOP, with similar results.[45] However, there is still a lack of evidence and further studies are needed to confirm the effectiveness and safety of high flow nasal cannula in the treatment of AOP.[46]

Mechanical ventilation

When noninvasive ventilation strategies are not effective, endotracheal intubation and mechanical ventilation should be considered.

Environmental temperature

Temperature values on the lower limits of the range seem to be associated with lower apnea rates,[47] so overheating should be avoided, even if more studies are needed to confirm this observation.

Kangaroo mother care

The effectiveness of this approach for the prevention or treatment of AOP remains controversial. A randomized controlled trial showed a reduction in apnea and bradycardia in infants receiving kangaroo care.[48] No differences in apnea rates were seen in another study when compared with prone positioning.[49]

Supplementation with branched-chain amino acids

The increased work of breathing in preterm infants, due to the highly compliant chest wall, may lead to muscle fatigue that contributes to AOP. Parenteral nutrition enriched with branched-chain amino acids, which improve diaphragmatic function in vitro,[50] could improve diaphragmatic strength. However, further evidence is needed to confirm this hypothesis.

Oral sucrose

Despite the analgesic effect of oral sucrose and pain being a stimulus for apnea, administration of oral sucrose has not been found to be effective in reducing the number of desaturations and bradycardias compared with placebo.[51]

Tactile stimulation

Tactile stimulation from a special mattress with embedded actuators that deliver small stochastic displacements achieved a 65% reduction in duration of oxygen desaturation.[52] Further studies are needed to confirm these results.

Olfactory stimulation

It has been observed that odors can modulate the respiratory pattern of preterm infants, particularly during active sleep, when apnea is more common. In a group of 14 infants with GA 24–28 weeks who were unresponsive to both caffeine and doxapram, it was found that exposure to 15 drops of saturated vanillin solution applied on the periphery of the infant's pillow led to a 45% reduction in the frequency of apnea associated with bradycardia.[53]

Red blood cell transfusion

There is currently no clear evidence that red blood cell transfusions can influence the course of AOP. The reduction in oxygen transport that occurs during anemia may have a role in the onset or worsening of AOP, considering also the immature responses to hypoxia of the preterm infant. Studies have yielded conflicting results with regard to the effect of red blood cell transfusion on the incidence of apneas. A recent study evaluated 67 very low birth weight infants (weighing ≤1,500 g) without or with minimal respiratory support (spontaneous breathing in room air or with oxygen in the cot, or nCPAP, but not intubated) and who have received one or more red blood cell transfusions (median 1, range 1–6). Transfusion of packed cells was followed by a statistically significant reduction in number of apneas. The likelihood of having apnea in the 12 hours following transfusion was related to hematocrit.[54] Despite not being able to consider red blood cell transfusion as a treatment for moderately anemic infants with AOP, this option should be evaluated on a case by case basis.

Pharmacological treatment

Caffeine and methylxanthines

The drugs most commonly used for treating and preventing AOP are the methylxanthines, such as caffeine, theophylline, and aminophylline. Caffeine should be considered as the drug of first choice for AOP. Methylxanthines are endogenous adenosine antagonists (ie, central respiratory depressants, but also have peripheral respiratory stimulant activity). The main effect of xanthines is therefore to increase the output of the respiratory center, which determines an increase in ventilation. Theophylline is generally less well tolerated, causing tachycardia and gastrointestinal disturbances, and the relationship between therapeutic and toxic doses is weaker than for caffeine, so theophylline is not routinely used anymore.

The efficacy of caffeine in the treatment of AOP was discovered back in 1977 by Aranda et al, who observed a reduction of apnea episodes in 18 neonates with a GA of <28 weeks and treated with an initial bolus dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg.[55] After more than 30 years, Aranda et al refer to caffeine as the "silver bullet in neonatology" because it is one of the safest and most effective drugs and has the best cost/benefit ratio of all the agents used in neonatology. The trial with the largest number of preterm neonates was that by Schmidt et al.[56,57] It was a multicenter, randomized, placebo-controlled trial for which the authors recruited nearly 1,000 neonates weighing 500–1,250 g. The caffeine group was treated with standard doses (20 mg/kg/day via bolus followed by 5 mg/kg/day) from the GA of 28–35 weeks, with an average treatment duration of 37 days. Schmidt et al demonstrated that treatment with caffeine reduces the durations of continuous positive airways pressure and oxygen administration. In the caffeine group, use of postnatal steroids and need for red blood cell transfusions were also reduced. The recommended caffeine dose

when treating AOP is 20 mg/kg given as a bolus followed by a maintenance dose of 5 mg/kg/day, which can be increased if treatment is unsuccessful. Some investigators have demonstrated that higher doses have a better effect on apneas when compared with lower doses.[58] However, there are not enough data in the literature to support the use of caffeine in preterm infants for prevention of apnea.[59]

Unresolved issues with caffeine

One of the problems not addressed in the literature, and still unresolved, is the duration of treatment with caffeine. It is observed in clinical practice that preterm infants with AOP are often continued on caffeine until 36 weeks PMA, even if they have not had episodes of apnea for several weeks. When is the right time to stop the caffeine? Early suspension of treatment can be attempted or it is likely to result in a return of apnea and therefore a return to treatment? At what GA is it appropriate to make such an attempt? Probably, despite the proven positive effects of caffeine on bronchopulmonary dysplasia,[56] many preterm infants who have not yet reached 36 weeks of PMA and have no oxygen requirement may suspend caffeine treatment safely.

Rhein et al recently evaluated the frequency of intermittent hypoxia in premature infants after discontinuation of routine caffeine therapy and assessed whether extending treatment to 40 weeks PMA reduces these events. They found that intermittent hypoxia events persist after discontinuation of routine caffeine treatment and decrease progressively with increasing PMA. Intermittent hypoxia events were also decreased in infants for whom caffeine treatment was extended.[60]

Some studies have reported a reduction in cerebral and intestinal blood flow in the first 2 hours after administration of caffeine, risk factors for the development of cerebral hemorrhage and necrotizing enterocolitis.[61] However, the trial by Schmidt et al showed no significant differences in rates of necrotizing enterocolitis and brain injuries between infants treated with caffeine and infants who received placebo. Meanwhile, in the caffeine group, rates of bronchopulmonary dysplasia and cerebral palsy were lower, and a higher survival without neurodevelopmental disability was observed.[56,57]

A very recent study investigated the incidence of side effects (tachycardia, seizures, gastric residuals, vomiting, necrotizing enterocolitis) occurring with use of a licensed product or extemporaneous caffeine citrate. The authors demonstrated a similar safety profile for both formulations of caffeine citrate, but extemporaneous caffeine citrate was associated with a significantly higher risk of necrotizing enterocolitis.[62] However, these results must be viewed with caution because this was not a randomized controlled trial and not all factors potentially causing necrotizing enterocolitis were considered.

Although caffeine is generally a well tolerated agent, signs of overdose, severe tachyarrhythmia, irritability, jaundice, food intolerance, and polyuria, must be recognized. Fever, tachypnea, hypertonicity, vomiting, hyperglycemia, and even seizures may appear at caffeine levels >50 µg/mL. Measurement of plasma caffeine levels is not routinely necessary, but may be useful in the event of symptoms suspicious for overdose or when therapeutic doses higher than those commonly prescribed are needed.

During caffeine therapy, attention should be paid to other medications that can interfere with its metabolism; phenytoin and phenobarbital may increase elimination of caffeine, so cotreatment typically requires higher doses of caffeine. Caffeine is an antagonist of adenosine receptors, so higher doses of adenosine may be required to treat tachyarrhythmia while on treatment with caffeine.

A recent study investigated the effects of early initiation of caffeine on bronchopulmonary dysplasia and mortality in a broad population of very low birth weight infants. The results showed that when therapy was started early (in the first 3 days of life), there was a reduced incidence of bronchopulmonary dysplasia.[63]

Doxapram

Doxapram is a potent stimulator of breathing, stimulating peripheral chemoreceptors at low doses and central chemoreceptors at high doses. Its effect in reducing apnea is directly related to the dose administered. Its use in neonates has been performed in limited and uncontrolled case series. The dose of doxapram reported to be effective for apnea is 2.5 mg/kg/hour given by continuous intravenous infusion, although the trend is to give lower doses (maximum 1.5 mg/kg/hour).[64] It is rarely administered orally, but if so, should be given with tube in one hour (every 8 or 12 hours).[65] Possible side effects during infusion include jaundice, convulsions, myoclonus, irritability, increased blood pressure, and increased gastric residuals. Three cases of atrioventricular block have also been reported.[66] The most important and potentially dangerous side effect is decreased cerebral oxygenation and blood flow velocity. This might result in decreased cerebral perfusion and damage to the developing brain, leading to long-term developmental delay.[67] Therefore, doxapram is not currently recommended for the treatment of AOP.

Resolution of AOP and consequences

Although AOP is, by definition, a self-limiting disease and resolves with advancing PMA, it can cause not only acute problems but also an increased risk of impaired neurological development and/or retinopathy of prematurity, especially in preterm infants of lower GA in which the course of AOP is prolonged. Apneas persisting beyond 38 weeks are seen more frequently in infants born at a GA of 24–27 weeks than in those born at a GA of 28 weeks.

Studies have not yet clarified the frequency and severity of episodes of desaturation and bradycardia associated with an increased risk of neurological damage. In preterm neonates, oxygen desaturation/bradycardic episodes can cause alterations in cerebral hemodynamics that may compromise the subsequent neural development of the neonate. However, it is hard to demonstrate a direct correlation between the two phenomena, given all the conditions associated with a potentially negative effect on the neurological outcome of this category of infants. In fact, the frequency and severity of apneas leading to an increased risk of neural damage has not been established. In a trial conducted in 175 neonates born at a GA of <32 weeks or weighing less than 1,250 g who were monitored up to 3 years of age, Janvier et al found that the number of days of apnea and male sex were significantly associated with an increased probability of altered neural development.[68]

Resolution of apneas and demonstration of an apnea-free period are necessary before a preterm infant can be discharged without being prescribed an apnea monitor at home. The apnea-free period, after which it can be assumed that the infants are unlikely to have another apnea episode, need to be individualized, taking into account infant's GA and PMA and the PMA of the last event. However, generally, in the absence of other risk factors, 8 days or more, can be considered a reasonable apnea-free period before discharge, even after discontinuation of caffeine. This is because the half-life of caffeine is 3–4 days, but may be extended in special circumstances, as in the case of cholestatic hepatitis. Autonomous feeding and thermoregulation in an open cradle correlate closely with resolution of AOP.

Conclusion

AOP is a developmental disorder and is, by definition, self-limiting. However, it can cause serious problems during the hospital stay and potentially have long-term neurological and cognitive consequences, despite the lower limit beyond which hypoxemia and/or bradycardia increase the risk of impaired neurological development having not yet been identified. The apnea can be defined as idiopathic only after excluding a number of diseases of the preterm infant in which apnea may be an epiphenomenon. The etiological diagnosis is critical for specific treatment. Idiopathic apnea may require use of drugs, but can sometimes resolve with nonpharmacological intervention. Treatment should be individualized according to the weight and GA of each infant, taking into account any associated conditions. The first approach usually should be prone, 15-degree, head-up positioning; if the apnea persists, treatment with caffeine should be initiated, and in the event of persistence of severe or frequent apneic episodes, ventilatory support with nCPAP/nSIPPV should be commenced. Caffeine should be started early in preterm infants at a GA of <28 weeks or when body weight is <1,250g. Intubation and mechanical ventilation should be considered in the event of AOP that does not respond to the proposed treatments.

Despite treatment with caffeine having been shown to be safe and effective, doubts remain about its use. It has not yet been established how long treatment with caffeine should be continued if the infant has ceased to have apneas. Precisely when to discontinue the drug, particularly in newborns with no oxygen requirement, has yet to be established. Moreover, it remains unclear whether caffeine can alter, even temporarily, cerebral or intestinal blood flow and thus promote intraventricular hemorrhage or necrotizing enterocolitis. Therefore, the safety of drugs such as caffeine and doxapram should be investigated further. Also, more recently proposed interventions with theoretical benefits that still need to be demonstrated, such as branched-chain amino acids and tactile/olfactory stimulation, warrant further studies and need data to prove their effectiveness. Particular attention should be paid to the monitoring of preterm infants, given the different thresholds for treatment between centers on the basis of the alarm limits and the averaging times (duration of filters used to minimize motion artifacts) set on the pulse oximeters. Further research is needed to understand better the long-term outcomes in infants with AOP, as well as the severity and frequency of apnea episodes that may be tolerated in order to avoid possible overtreatment in already fragile and stressed infants.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit-sectors. The authors report no conflict of interest in this work.

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