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Review Article

Apnea in Neonates - Concepts and Controversies

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Abstract

Apnoea of prematurity (AOP) is a common problem affecting premature infants. Apnoea is defined as cessation of breathing for more than 20 seconds or for lesser duration when associated with bradycardia and desaturation. The most likely and accepted pathogenesis is the "physiologic" immaturity of respiratory control in the neonates. The physiological immaturities include altered ventilatory responses to hypoxia, hypercapnia, and altered sleep states. Other hypotheses include gastroesophageal reflux and anaemia which are still controversial. Three types have been identified namely obstructive, central and mixed types of apnoea. Management options include the use of supplemental oxygen, position chages and drug therapy with methyxanthines. Other supportive therapies include kangaroo care, packed cell transfusions. The long term neurodevelopmental consequences of AOP and its treatment still needs to be studied further..

Keywords: Apnoea of Prematurity; Premature Infant; Neurodevelopment; Methylxanthine Therapy

Introduction

Prematurity is associated with problems of temperature regulation, acquisition of oral feeding skills, and immature control of respiration leading to apnoea [1]. Resolution of apnoea and establishment of a normal respiratory pattern is a major developmental milestone for premature infants. The accepted definition of apnoea of prematurity (AOP) defines it as cessation of breathing for more than 15-20 seconds, or accompanied by oxygen desaturation (SpO_2≤80% for ≥4 seconds) and bradycardia (heart rate<100) [2]. Pathogenesis AOP is linked to the developmental immaturity of the respiratory control of breathing and it resolves on its own over period of time. AOP reflects a "physiological" rather than a "pathological" immature state of respiratory control.

Incidence

The incidence of AOP is inversely correlated with gestational age and birth weight. Seven percent of neonates born at 34 to 35 weeks gestation, 15% at 32 to 33 weeks, 54% at 30 to 31 weeks and nearly all infants born at 28 weeks develop apnoea. Apnoea is classified into three subtypes: central, obstructive, or mixed. Central apnoea accounts for approximately 10% to 25% of all cases of apnoea, with obstructive apnoea accounting for 10% to 25% and mixed for 50% to 75% [3,4].

Fetal to Neonatal Transition

The fetus moves from an oxygen-poor hypoxic environment in utero where the PaO_2 is 25-27 mmHg, to an oxygen-rich environment after birth. The postnatal rise in PaO_2 effectively reduces the sensitivity of the peripheral chemo receptors, resulting in delayed onset of spontaneous respiratory efforts when neonates are exposed to 100% oxygen during postnatal resuscitation. Hence the neonates need adapt to the postnatal environment by altering the respiratory and ventilator controls. But because of the immature respiratory control pattern and chemoreceptor function in premature infants there is a delay in this adjustment [5].

Ventilatory Response to Hypoxia

The ventilatory response to hypoxia after birth in premature infants elicits an initial transient increase in respiratory rate and tidal volume that lasts for 1-2 min, followed by a late, sustained decline in spontaneous breathing that may last for several weeks. This late decline in spontaneous breathing is termed hypoxic ventilatory depression, which could be associated with the delayed postnatal respiratory adjustment [6]. Peripheral chemoreceptor stimulation may also lead to apnoea secondary to hypocapnia seen after hyperventilation. The apnoeic threshold of CO_2 secondary to

hyperventilation along with peripheral chemoreceptor activation in response to hyperventilation may lead to apnoea [7].

Ventilatory Response to Hypercapnia

Preterm infants increase ventilation by prolonging the period of expiration, but not increasing breath frequency or overall tidal volume, leading to less minute ventilation in response to hypercapnea. This poor hypercapnic ventilatory response is more pronounced in premature infants with apnoea than without apnoea [8]. Contradictory movements of respiratory muscles in response to hypercapnia may also play a role in AOP.

Ventilatory Responses to Laryngeal Chemoreflex

Activation of the laryngeal mucosa in premature infants can lead to apnea, bradycardia, and hypotension. While this response is assumed to be a protective reflex, an exaggerated response may cause AOP. This reflex-induced apnea is termed the laryngeal chemoreflex and is mediated through superior laryngeal nerve afferents [9].

Neurotransmitters and Apnoea

Enhanced sensitivity to inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), adenosine has been postulated as a pathogenic mechanism. GABA is the major inhibitory neurotransmitter in the CNS. Adenosine is a product of adenosine triphosphate and is formed as a consequence of metabolic and neural activity in the brain, especially during hypoxia. Reports have found an interaction between adenosine and GABA in the regulation of breathing. This association is further strengthened by the observations that adenosine receptors are expressed in GABA-containing neurons. The binding of adenosine to its receptor may be involved with the release of GABA and thus inhibit respiration leading to apnoea [10].

Genetic Variability and Apnoea

Tamim et al. [11] reported a higher proportion of first degree mating for infants with AOP compared with those without AOP. Further need to be done in this area to give a clear conclusion regarding the genetic factors role in AOP.

Effects of Sleep State and Movements on Apnoea

Premature infants spend a large proportion of their time in rapid eye movement (REM) sleep, with a relatively smaller amount in wakefulness. During REM sleep, these infants have more paradoxical breathing with a less stable baseline of oxygen saturation. Therefore, apnoea occurs more frequently in REM sleep than in quiet sleep12. Arousal from REM sleep appears to be a precursor to apnoea associated with oxygen desaturation in premature infants since motor activities after arousal are typically associated with laryngeal closure. Therefore, movements frequently precede or occur simultaneously with apnoea, and arousal from sleep may cause the apnoea rather than terminate it [12,13].

Other Factors Involved in Apnoea

While immature respiratory control is the primary cause of apnoea in the premature infant, many coexisting factors can potentiate or worsen apnoea. Apnoea is a common presenting sign of both local and systemic infection13. Apnoea can be secondary to central nervous system diseases like intracranial haemorrhage, hypoxic-ischemic encephalopathy, and seizures. Exposure to cooler temperatures decreased the duration and frequency of AOP, while elevated body temperature increased the incidence of AOP, suggesting that apnoea is related to metabolic state and environmental temperature [1,2]. Other factors that have been associated with apnoea in premature infants include glucose or electrolyte imbalance, presence of a hemodynamically significant patent ductus arteriosus (hs-PDA) [1,2]. Anaemia is also associated with apnoea because of lowered oxygen-carrying capacity of red blood cells that leads to hypoxia, resulting in respiratory depression. Drugs including narcotic analgesics and magnesium sulfate, can lead to apnea in infants. The role of Gastroesophageal reflux in causing apnoea is controversial also, there is no evidence to support the use of anti-reflux medications for the prevention of aponea [14].

Interventions for Premature Infants with Apnoea

Interventions for AOP include efforts to reduce work of breathing and/or increase respiratory efforts.

Non Pharmacological Therapies

Prone Position

Prone positioning can improve thoracoabdominal synchrony and stabilize the chest wall without affecting breathing pattern or SpO_2. Several studies have demonstrated that prone position reduces AOP [15]. Extension of the neck 15° from the prone position is referred to as the head -tilt position, which has been found to decrease episodes of oxygen desaturation and it should be considered as a first-line intervention in infants with AOP However, head- tilt position has not been shown to work in combination with pharmacologic therapy.

Continuous Positive Airway Pressure and Nasal Intermittent Positive Pressure Ventilation

CPAP at 4-6 cm H_2O has proven a safe and effective therapy for AOP. CPAP delivers a continuous distending pressure via the infant's pharynx to the airways to prevent both pharyngeal collapse and alveolar atelectasis [16]. Therefore, CPAP can enhance functional residual capacity and reduce the work of breathing, improving oxygenation and decreasing bradycardia. CPAP works effectively to reduce the incidence of obstruction, but it has no clear efficacy in central AOP. An extension of CPAP is the administration of NIPPV which has been shown to be more effective than CPAP in preventing extubating failure and for the treatment of AOP [17].

Other Therapies

KMC

Maternal kangaroo care, also known as skin-to-skin care for premature infants, has calming effects on the baby's clinical status and vital signs. It has shown to be effective in reducing the apnoea [18,19].

Sensory Stimulation

Several studies suggest that sensory stimulants, including tactile and olfactory stimulation, are useful in the treatment or prevention of AOP. Tactile stimulation is the most common intervention in response to AOP. This simple intervention most likely works by generating excitatory, nonspecific neuronal activity in the brainstem centre to stimulate respiratory activity. However, cutaneous stimulation often arouses the infant and markedly affects breathing pattern in premature infants. Systematic review has shown that kinesthetic stimulation is not effective at preventing AOP [20]. Olfactory stimulation has also been used for the treatment of AOP. Pleasant odors elicited increased respiratory drive, whereas unpleasant odors caused decreased respiratory effort, during active sleep when apnoea is more common. Vanillin, a stimulus known to affect the olfactory nerve, was used to treat refractory apnoea and bradycardia unresponsive to both caffeine. Studies have concluded that the presence of a pleasant odour helped the infants to better regulate their respiratory patterns [21]. CO_2 inhalation, CO_2 is the physiologic stimulus for breathing in mammals. Apnoea occurs when the CO_2 baseline decreases below the apnoea threshold. A rise in CO_2 of 1 to 2 mmHg above the apnoea threshold will reduce or abolish apnoea. Recently, a randomized controlled trial of theophylline versus CO_2 inhalation for treating AOP showed that inhalation of a low CO_2 concentration (0.8%) in premature infants is as effective as theophylline in decreasing apnoea. This exposure to 0.8% CO_2 also had no effect on cerebral blood flow velocity. The authors concluded that CO_2 may be a better treatment for AOP than methylxanthines. However, it is likely that infants will quickly accommodate to an inspiratory CO_2 concentration, and the effectiveness of long-term exposure is not known [22]. An increase in upper airway resistance may also play a significant role in AOP. Nasogastric tubes have been documented to increase nasal airway resistance by 50%. Therefore, orogastric feeding tubes are sometimes preferred in premature infants with apnoeic events. Interestingly, transpyloric feedings, especially when limited to human milk, have recently been shown to be safe and reduce episodes of apnoea and bradycardia in premature infants with suspected gastroesophageal reflux [23].

Thermoneutral Range

A mild increase in body temperature in infants enhances the instability of the breathing pattern. However, a specific environmental temperature to reduce the incidence or severity of AOP is not known, and more research is required.

Packed Cell Transfusion

Anemia can lead to AOP, and a proposed mechanism to treat AOP is transfusion of red blood cells to increase oxygen carrying capacity. However, data on the effect of blood transfusion on AOP is not clear. Because of the lack of clear cut evidence transfusion to treat AOP may not be recommended as a routine unless the neonate fulfils the recommened transfusion criteria for preterm neonates [24].

Methylxanthine Therapy

Methylxanthine compounds such as caffeine, theophylline, and aminophylline have been administered to premature infants as respiratory stimulants to decrease AOP. These drugs are powerful central nervous system stimulants and are likely to reduce apnea by multiple physiological and pharmacological mechanisms [25,26].

These drugs are antagonist of adenosine receptor and work by increasing the minute ventilation, improving the CO_2 sensitivity and neural respiratory drive and decreasing the hypoxic respiratory depression. Other mechanisms include improved diaphragmatic contraction and improved respiratory muscle function [25]. Systematic reviews of caffeine therapy in AOP have shown that both caffeine and theophylline are effective in reducing apnoea. Caffeine is the preferred of the two drugs considering its wider therapeutic range and the plasma half-life making it ideal for once a day administration. Further studies have shown that the incidence bronchopulmonary dysplasia and neurodevelopment disabilities have decreased with the use of Caffeine. The potential mechanism of neuroprotection is not clearly understood but could be explained by the decrease of ventilator-induced lung injury (VILI) due to the use of caffeine [26-28]. Caffeine is usually available as caffeine citrate and the active component comprises of only 50% of the total dose. Caffine is generally given as a loading dose of 10 mg/kg caffeine (i.v. or orally) followed by a maintenance dose of 5 mg/kg once daily. Higher doses have been studied but have shown to be of little use except in cases of refractory AOP [27,28].

Theophylline is usually recommended at a loading dose of 5-6 mg/kg, followed by maintenance doses of 2-6 mg/kg/day in divided into two or three daily doses. Therapy with methylxanthines is associated with few adverse events. Toxic levels may produce tachycardia, cardiac dysrhythmias, and feeding intolerance or, at very high doses, may precipitate seizures. Mild diuresis and delayed gastric emptying can also be seen in very low birth weight infants on methyxanthine therapy. Methylxanthines also increase energy expenditure, possibly leading to diminished growth in premature infants hence a extra caloric requirement is necessary in infants treated with theophylline [26-28]. Doxapram is a potent respiratory stimulant previously used for the management of apnoea refractory to methylxanthine therapy. The use of doxapram is controversial because of its reported adverse effects with include irritability, elevated blood pressure, and gastric retention, increase in cerebral oxygen consumption and a decrease in oxygen delivery. This is probably mediated by a decrease of cerebral blood flow. Therefore, doxapram is not routinely recommended for AOP since its side effects and long-term benefits versus potential harm are concerning [29]. Drugs are generally stopped when the neonate is apnoea free for 7 days or has reached 34 weeks Corrected gestational age and it is generally advisable to stop the drugs 4 to 5 days prior to discharge of these neonates as the drugs have long half-life and premature discharge after stopping the drugs may lead to dire consequences.

Consequences of AOP

It is difficult to prove a link between apnoea and poor neurodevelopment outcomes due to the possible coexistence of neurological injury in premature infants. In early studies, no differences in neurodevelopment outcomes were found between AOP and control infants [30,31]. Janvier et al30. found that an increased number of AOP days were associated with neurodevelopment impairment such as cerebral palsy and blindness at 3 years of age. Recently, researchers found that a higher frequency and severity of AOP were associated with a higher incidence of unfavorable outcomes or death. Possible explanation for this is that multiple recurrent hypoxic and bradycardia following AOP may cause long-term cerebral dysfunction. Apnoea is a very common symptom in premature infants. Treatment options include pharmacological and physical and sensory stimulation. The long-term consequences of severe, recurrent apnoea-associated bradycardia and desaturation still needs to be studied in detail in future studies.

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