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Successful Use of Caffeine Citrate for Neonate With Bronchiolitis-Related Apnea: Case Report and Clinical Insights

Abdulla Alfraij | Ahmed Aboalazm

Pediatric Intensive Care Unit, Department of Pediatrics, General Ahmadi Hospital, Kuwait Oil Company (KOC), Ahmadi, Kuwait

Correspondence: Abdulla Alfraij (alfraij.abdulla@gmail.com)

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ABSTRACT

To date, there is no clear evidence supporting the use of caffeine therapy in bronchiolitis-related apnea in pediatric intensive care units. Generalizing the approach for all bronchiolitis cases could be behind this limitation of the evidence. Here, we report a successful use of caffeine citrate for a neonate with bronchiolitis-related apnea. Understanding the limitations of case reports, we think being a neonate diagnosed with bronchiolitis-related apnea without respiratory distress, on top of a prematurity background, might be the key characteristic for this successful use.

1 | Introduction

Bronchiolitis is one of the most common seasonal diseases in pediatrics under 2 years of age, with an overall incidence of 11%–15% [1]. It is caused by a viral infection, predominantly by respiratory syncytial virus (RSV), which leads to lower respiratory tract symptoms [2]. One of the serious complications of bronchiolitis is apnea, which has an incidence of approximately 20% in infants younger than 6 months [2, 3]. Apnea is known as cessation of breathing or airflow obstruction for more than 20 s; less duration could also be considered apnea if it is associated with clinical manifestations like bradycardia, hypoxemia, cyanosis, pallor, or hemodynamic instability [4]. The main risk factors for apnea in bronchiolitis include prematurity up to the corrected age of 2 weeks, low birth weight of less than 2300 g, and previous history of apnea episodes [3]. The cornerstone of bronchiolitis treatment is supportive, that is, ensuring oxygenation and providing nutritional support. Respiratory support is warranted in infants presenting with moderate to severe bronchiolitis as these infants may go into respiratory failure. To date, there is no strong evidence supporting medical treatment for bronchiolitis-related apnea requiring intensive care apart from supportive respiratory measures [5].

Caffeine, a central respiratory drive stimulant, is a well-known safe therapy and one of the lines for treatments of apnea of prematurity [4, 6, 7]. It has become a standard of care for most neonatal units in premature babies' care, especially for those who are less than 28 weeks gestation [8]. The discontinuation time for the caffeine therapy in those babies is still not well determined; however, some protocols support discontinuing the therapy whatever of the following comes first: if the baby becomes apnea-free for five to 7 days without positive pressure ventilation or once reaching 33–34 weeks postmenstrual age [4]. The approach of using caffeine therapy in bronchiolitis cases with apnea was extrapolated for the premature babies' evidence. An eight-year retrospective cohort study conducted by Heuzé and his group found that the apnea-induced bronchiolitis cases

Abbreviations: BiPAP, bi-level positive airway pressure; CBC, complete blood count; CRP, C-reactive protein; ED, emergency department; PCT, procalcitonin; PEEP, positive end-expiratory pressure; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection; WBC, white blood count.

Summary

- Bronchiolitis is a common disease that might be complicated by apnea.
- Using caffeine therapy for premature non-distress neonates with apnea due to bronchiolitis may influence its successful use, though well-controlled studies are required to guide this practice.

receiving caffeine therapy had a shorter length of hospital stay but not pediatric intensive care unit (PICU) stay [5]. A single-dose caffeine therapy randomized controlled trial by Alansari et al. [9] failed to show a significant reduction in bronchiolitis-related apnea. Unfortunately, the literature could not generate an evidence-based guideline for using caffeine therapy for bronchiolitis-related apnea in PICU [10]. Here, we present a neonate in our PICU with bronchiolitis-related apnea who responded successfully to caffeine citrate therapy with a three-dose regimen.

2 | Case History/Examination

A 21-day-old female baby, with a corrected gestational age of 36^{+2} weeks and a weight of 2.280 kg, was brought to the emergency department (ED) at General Ahmadi Hospital following an episode of apnea at home. The parents reported a two-day history of upper respiratory tract infection (URTI) symptoms, including sneezing, along with sick contact exposure with similar symptoms. There was no history of fever, vomiting, or cough; however, the mother noted a reduction in the baby's activity in the last few hours prior to the presentation, which was associated with cessation of breathing. Upon examination in the ED, the baby appeared well-hydrated, without signs of respiratory distress (respiratory rate was 36 breaths per minute), maintaining oxygen saturation at 99% on room air, and demonstrated good perfusion with stable hemodynamics. The rest of the clinical examination was consistent with a well-looking baby. The patient was initially admitted to the pediatric ward with a diagnosis of apnea for investigation—to rule out sepsis. During her stay in the ward, she experienced a significant episode of apnea that lasted for about 3 min, which required a positive pressure ventilation using a bag and mask. Though she returned to a normal breathing pattern with normal oxygen saturation in room air, she was transferred to the PICU for close monitoring and further respiratory support. The baby was placed on Bilevel positive airway pressure (BiPAP) support with a peak inspiratory pressure of 12, positive end-expiratory pressure (PEEP) of 6, a respiratory rate set at 40, and FiO_2 21%–40%. Her blood gases and oxygen saturation remained within a normal range throughout. While on BiPAP, the baby experienced two episodes of significant apnea, as evidenced by BiPAP alarms, significant bradycardia, absence of respiratory effort, and desaturation upon clinical assessment despite a well-fitted BiPAP mask.

Reviewing her neonatal history, the patient is one of a set of preterm twins, born at 33^{+2} weeks gestation, with good APGAR scores and a birth weight of 2070 g. Following delivery, she was admitted to the neonatal unit, where she received non-invasive ventilation for 1 day, followed by high-flow nasal cannula support for 2 days. Afterward, she remained on room air for about 9 days. She was started routinely, that is, without any apnea episodes, on caffeine citrate from day one of life (in accordance with our neonatal unit policy) which continued for a total of 4 days only as she reached 34 weeks of corrected gestational age, after which it was discontinued. No episodes of apnea were observed from birth, during her stay in the neonatal unit, or at home until her recent presentation to our ED at the age of 21 days.

3 | Differential Diagnosis, Investigations, and Treatment

Initial investigations in the ED revealed normal capillary blood gas results, with a pH of 7.38, pCO_2 of 41.2 mmHg, pO_2 of 64.9 mmHg, and HCO_3 of 23.6 mmol/L. A basic blood workup, including a complete blood count (CBC) and kidney profile (Table 1), was also within normal ranges except for a slight rise in the serum inflammatory markers (C-reactive protein and procalcitonin), which can also be seen in some bronchiolitis cases. An unremarkable chest X-ray supported the bronchiolitis diagnosis (Figure 1). A head ultrasound was performed and reported to be normal. Furthermore, a full septic workup was carried out, which yielded unremarkable results. She was empirically started on cefotaxime and ampicillin until negative cultures resulted after 48 h of incubation. Other differential diagnoses, such as congenital cardiac defects, pneumonia, and seizures, were excluded based on the patient's history, clinical examination, and initial workup, including echocardiogram. A nasopharyngeal swab confirmed the presence of RSV, supporting the diagnosis of bronchiolitis complicated by apnea.

Although intubation and mechanical ventilation were considered (given the BiPAP failure); however, her history of

TABLE 1 | Initial blood work results for the patient.

Test (unit)	Result
White blood count (WBC)	9.5×10^9/L
Hemoglobin	14.9 g/dL
Platelet count	421×10^9/L
C-reactive protein (CRP), quantitative	28.6 mg/L
Procalcitonin (PCT)	1.04 ng/mL
Sodium	137 mmol/L
Serum potassium	4.3 mmol/L
Chloride	100 mmol/L
Blood urea nitrogen	2.5 mmol/L
Creatinine	32 μmol/L
Glucose	4.6 mmol/L
Corrected calcium level	2.37 mmol/L
Phosphorous level	1.71 mmol/L
Magnesium level	0.93 mmol/L
Albumin	41 g/L

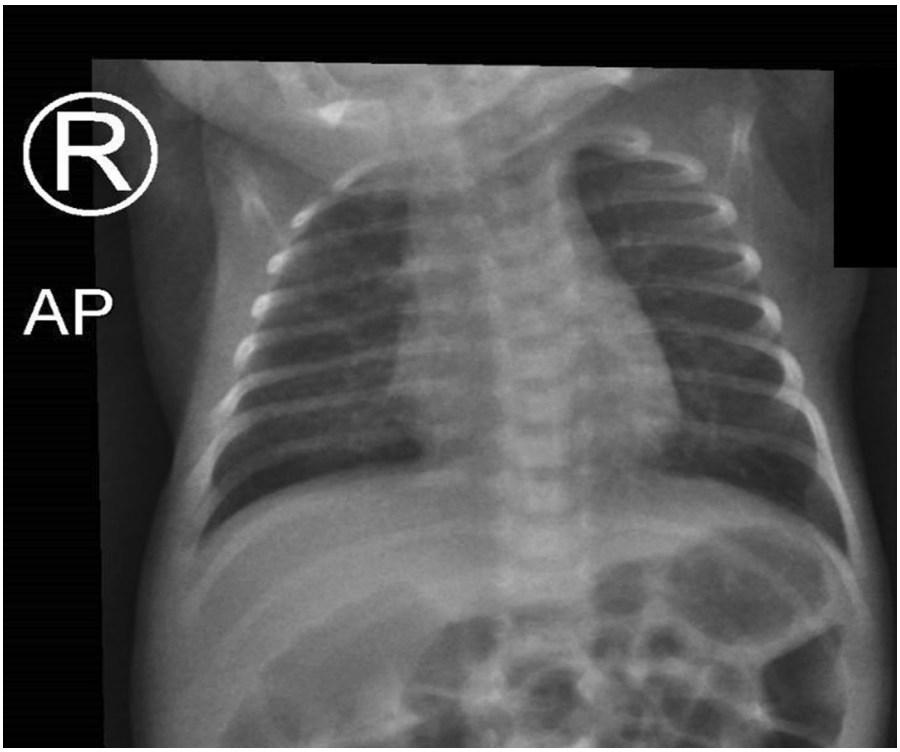

FIGURE 1 | Admission chest X-ray for the case.

prematurity and normal clinical examination between the episodes and investigations led to considering caffeine therapy as an option. Thorough discussion with her parents about the possibilities, potential benefits, and risks of caffeine therapy was reviewed, including the limited evidence supporting its use in such cases and the possibility of treatment failure; therefore, the need for intubation at any stage. From which, caffeine citrate was initiated at a dose of 2.5 mg/kg once daily for 3 days under close monitoring.

4 | Outcome and Follow-Up

Following the initiation of caffeine citrate, no further apnea occurred, and BiPAP support was successfully weaned off to an oxygen nasal cannula within 24 h post-caffeine treatment. Two days of observation on a nasal cannula followed by 2 days on room air (off caffeine therapy) confirmed the absence of apnea. She was discharged from the PICU, with a total stay of 5 days (a day on BiPAP overlapped with 3 days on caffeine citrate and 2 days of observation on room air). The patient was discharged home with no further recurrence of apnea and followed up in the outpatient clinic for 2 months, where there was no recurrence of apnea.

5 | Discussion

Bronchiolitis-related apnea remains one of the main reasons for the use of mechanical ventilation in infants diagnosed with bronchiolitis. Multiple mechanisms are behind bronchiolitis-related apnea, including airway obstructive mechanisms (obstructive apnea), depression of the respiratory center in the brain (central apnea), or a combination of both mechanisms (mixed apnea) [9, 11]. In infants and young children, obstructive apnea is mostly attributed to the increase in mucous secretions and inflammation of the airways. On the other hand, the mechanism of central apnea in bronchiolitis is still not well clarified, though the literature supports the theory of the infection effect on the laryngeal chemoreceptors as an inflammatory response to the virus, commonly seen with RSV cases [11, 12]. Another mechanism is the impact of virus-specific suppressant proteins causing depression in the respiratory center in young babies [9]. The usual intervention in the PICU for such cases is to support their respiratory system invasively or non-invasively, which might prolong their stay in the intensive care unit.

Caffeine therapy increases the central respiratory drive and chemoreceptor sensitivity to carbon dioxide [6, 13]. Furthermore, it improves skeletal muscle contractions and reduces diaphragmatic fatigue, leading to better ventilation [6, 13]. Theoretically, caffeine citrate administration could reduce the duration and frequency of central apnea episodes, hence decreasing the length of stay in the PICU; however, Alansari et al.'s [9] RCT failed to prove this effect using a single-dose caffeine regimen. Caffeine citrate has a peak plasma concentration of an hour and a half-life of 5 h [6, 13]; this could explain the rapid response of our case to the therapy and the fast discontinuation of BiPAP. Generally, caffeine citrate is a safe drug as long as it does not reach the toxic threshold. Toxic levels might cause tachycardia, dysrhythmias, feeding intolerance, jitteriness, irritability, or seizures [13]. Using this therapy in our case was supported by the baby's background of prematurity and her condition as being hemodynamically and respiratory stable between the episodes. Besides, our consideration that the probable mechanism of her apnea is central, which we think is the key point for the treatment success

in our case. Though caffeine therapy could not reach significant evidence to be used in bronchiolitis-related apnea, the studied population and the doses regimen could considerably influence those results. We think that conducting RCTs with further stratifying the arms of the study to separate neonates with preterm backgrounds from full-term infants, and babies with apnea with respiratory distress vs. babies with apnea in the absence of respiratory distress might drive the evidence to show a benefit. More studies using this strategy might help better understand caffeine therapy's effect on bronchiolitis-related apnea cases.

6 | Conclusion

Using caffeine citrate in our bronchiolitis-related apnea case prevented the baby from intubation and being on a mechanical ventilator, which might have prolonged her PICU stay and put her at risk of mechanical ventilation-induced complications. Despite the lack of strong evidence and recommendations for using caffeine therapy in bronchiolitis-related apnea cases in the PICU, it might have some benefit in non-distressed bronchiolitis neonates with apnea, especially if a prematurity background is present, as in our case. Further research and studies are still required to increase our understanding and knowledge about this clinical practice.

Author Contributions

Abdulla Alfraij: conceptualization, data curation, methodology, project administration, supervision, writing – original draft, writing – review and editing. **Ahmed Aboalazm:** conceptualization, investigation, methodology, writing – original draft.

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The authors have nothing to report.

Consent

We confirm that written consent for the publication was obtained from the child's parents.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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