Caffeine for the Treatment of Apnea in Bronchiolitis: A Randomized Trial

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Objective To evaluate the efficacy and safety of caffeine citrate in the treatment of apnea in bronchiolitis.

Study design Eligible infants aged ≤4 months presenting to the main pediatric emergency service with apnea associated bronchiolitis were stratified by gestational age (<34 weeks or longer) and randomized to receive a single dose of intravenous 25 mg/kg caffeine citrate or saline placebo. The primary efficacy outcome was a 24-hour apnea-free period beginning after completion of the blinded study drug infusion. Secondary outcomes were frequency of apnea by 24, 48, and 72 hours after study medication, need for noninvasive/invasive ventilation, and length of stay in the hospital's pediatric intensive care/step-down unit.

Results A total of 90 infants diagnosed with viral bronchiolitis associated with apnea (median age, 38 days) were enrolled. The rate of respiratory virus panel positivity was similar in the 2 groups (78% for the placebo group vs 84% for the caffeine group). The geometric mean duration to a 24-hour apnea-free period was 28.1 hours (95% CI, 25.6-32.3 hours) for the caffeine group and 29.1 hours (95% CI, 25.7-32.9 hours) for the placebo group ($P = .88$; OR, 0.99; 95% CI, 0.83-1.17). The frequency of apnea at 24 hours, 24-48 hours, and 48-72 hours after enrollment and the need for noninvasive and invasive ventilation were similar in the 2 groups. No safety issues were reported.

Conclusions A single dose of caffeine citrate did not significantly reduce apnea episodes associated with bronchiolitis. *(J Pediatr 2016;177:204-11)*.

Trial registration Clinicaltrials.gov: NCT01435486.

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Viral bronchiolitis is the most common lower respiratory tract infection in infants, leading to 15 hospitalizations per 1000 person-years. Of these, 1.6% to 4% are admitted with apnea.[1-4] Bronchiolitis-associated apnea, a subset of apnea associated with respiratory viruses, appears to be a mixed central and obstructive apnea resulting from a complex interplay of respiratory drive suppression and airway secretions driven by a hyperactive laryngochemoreflex, somnogenic cytokines, and in some cases by virus-specific respiratory suppressant surface proteins.[5-7]

Caffeine is a standard treatment for apnea of prematurity[8,9] and postextubation apnea in preterm infants,[10] and has been used to ameliorate apnea complicating bronchiolitis on the basis of case reports and observational studies.[11-17] Caffeine increases central respiratory drive and chemoreceptor sensitivity to CO_2 and improves skeletal muscle contractions, reducing diaphragm fatigue and leading to better ventilation.[18] Increased metabolic demand, diuresis, tachycardia, dysrhythmias, feeding intolerance, reduced weight gain, and seizures are the reported short-term side effect of caffeine.[19] Although evidence from prospective studies for caffeine used to treat apnea in bronchiolitis is lacking, the drug is commonly used in an attempt to avoid intubation and is considered a standard of care in some institutions.[11,17,20] Thus, we compared blinded intravenous caffeine citrate with placebo for shortening the time to resolution of acute bronchiolitis-associated apnea.

Methods

This study involved a double-blind, randomized, parallel-group clinical trial of single-dose intravenous caffeine vs normal saline for the treatment of apnea in acute bronchiolitis (Clinicaltrials.gov: NCT01435486). The study was conducted during 3 bronchiolitis seasons in the infirmary/observation unit of the Pediatric Emergency Center of Hamad General Hospital, the sole pediatric emergency facility in the State of Qatar. The center serves an average of 280 000 outpatients annually and manages 45 beds in the infirmary/observation unit. All inpatient services are provided except intensive care. Patients with apnea and bronchiolitis are usually admitted to the pediatric intensive care unit (PICU) or a step-down unit for further observation and treatment. Patients who require invasive respiratory support, continuous positive airway pressure, and/or biphasic positive airway pressure are always admitted to the

PICU Pediatric intensive care unit

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PICU, and other patients can be admitted to either of the 2 areas based on bed availability.

Infants aged ≤4 months presenting with a provisional diagnosis of viral bronchiolitis associated with apnea were eligible for this study. This provisional diagnosis required apnea preceded by a prodromal history consistent with viral upper respiratory tract infection, with physical findings of bilateral chest crackles possibly associated with cough, rapid breathing, wheezing, and/or intercostal retractions. Out-of-hospital apnea was defined as witnessed sudden cessation of breathing associated with cyanosis and hypotonia within 6 hours before presentation, as reported by the caregiver. Apnea in the pediatric emergency center was defined as witnessed sudden cessation of breathing for >20 seconds or prolonged respiratory pause associated with cyanosis and/or bradycardia, as observed by medical staff.[21,22] Bradycardia was defined as heart rate <90 beats/minute. Patients were excluded who had 1 or more of the following characteristics: previous diagnosis of seizure disorder, gastroesophageal reflux disorder, suspected sepsis, previous history of renal or liver disease, known inborn error of metabolism, congenital heart disease or major congenital anomaly of the upper or lower respiratory tract, hypoglycemia or electrolyte abnormality on presentation, or receipt of caffeine treatment at home. Written informed consent was sought from a parent or legal guardian for each consecutive eligible patient as soon as the patient was admitted to the resuscitation room or short-stay unit. The study was approved by the hospital's Institutional Review Board.

Potentially eligible patients were examined on presentation in the emergency center, and those with an outpatient history of apnea were admitted to the infirmary/observation unit. All patients with observed apnea were admitted to the critical care areas for treatment. Patients were assessed for study eligibility within 30 minutes of the initial physician assessment, and after stabilization and enrollment were transferred to either the step-down unit or the PICU, based on bed availability and the need for invasive/noninvasive respiratory support.

All patients were connected to a cardiorespiratory monitor (MP70; Philips Healthcare, Andover, Massachusetts) in the emergency center and throughout their PICU/step-down unit stay, and to a portable cardiorespiratory monitor (MP30; Philips Healthcare) during transfer, set up to alarm outside the following values: respiratory rate, 20 to 60 breaths/minute, with a default apnea alarm delay of 20 seconds; pulse rate, 90 to 180 beats/minute; oxygen saturation, 90% to 100%. Caregivers did not wait for a monitor alarm, which served a safety backup function in most instances, before intervening with patients. Recording each episode of apnea witnessed with or without monitor alarm was required immediately after patient stabilization, on the data collection sheet and PICU/step-down diary of apnea record. Data on the occurrence of apnea were collected from patient records and data collection sheets daily.

Patients for whom consent was obtained underwent plain chest radiography and nasopharyngeal swabs for a rapid respiratory virus panel capable of identifying 20 respiratory viruses (multiplex real-time PCR assay on an ABI 7500 analyzer; Thermo Fisher Scientific, Waltham, Massachusetts). Randomization was stratified into 2 groups, patients born at <34 weeks gestation and those born at ≥34 weeks gestation.

The unblinded study pharmacist used a computer-generated randomization list[23] to prepare identical-looking numbered syringes containing either 15 mL of 0.9% sodium chloride or 25 mg/kg caffeine citrate diluted in D5W to make 15 mL of solution, to be infused intravenously by a syringe pump over 30 minutes. Inhaled therapies, supplemental oxygen, respiratory support, hydration, and other interventions were provided at the discretion of the treating physician. In 72 patients, venous blood gas analysis was requested by the treating physician, and samples were obtained within 30 minutes of arrival. All venous blood gas samples were obtained from an inserted intravenous infusion cannula in 1 of the 4 limbs from a free-flowing vein, collected in a microtainer tube at 500 μL. Samples were placed on ice immediately after extraction and sent to the department satellite laboratory for processing within 10 to 15 minutes.

A patient was transferred from the PICU/step-down unit to an ordinary inpatient pediatric bed when the treating physician determined that she or he was clinically stable, had no apnea in the preceding 24 hours, and was tolerating the start of feeding. The actual time of transfer could be delayed owing to lack of bed availability.

Study Outcomes

The primary efficacy outcome was time until a 24-hour apnea-free period beginning after completion of blinded study drug infusion. This is expressed as "time until last apnea episode" in our trial registration. An earlier proposed outcome, length of stay in the PICU, was changed before the start of study enrollment because it can be dependent on social factors and bed availability, unlike time until last apnea episode, which is measured objectively. Patients with a major protocol violation, such as receipt of caffeine in the placebo group or receipt of a second dose, were excluded in this proof-of-concept efficacy trial. Secondary outcomes were the frequency and duration of apnea in the first 24, 48, and 72 hours after study drug administration; invasive and noninvasive respiratory support administered; duration of oxygen therapy; time until feeding was tolerated; length of PICU/step-down unit stay; and overall length of hospital stay. As a safety measure, spot heart rate was compared every 4 hours from enrollment for up to 3 days.

Statistical Analyses

To estimate sample size, we performed a retrospective chart review of all patients admitted with apnea-associated bronchiolitis in 2010. A total of 87 patients who had not received caffeine were identified, of whom 52 (60%) were apnea-free at 12 hours after admission. We extrapolated these results to 24 hours because we did not have data for the proportion apnea-free at 24 hours. To enable detection of a 50% relative