Clinical Investigation

Apnea of Prematurity: Caffeine Dose Optimization

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OBJECTIVES The primary objective was to evaluate the correlation between maintenance dose and response rates in neonates less than 28 weeks gestational age. Secondary objectives included clinical indicators of response (number of weight adjustments, dose increases, and mini-loads) and tachycardia associated with caffeine therapy.

METHODS This study was a retrospective analysis of neonates admitted to the North Carolina Children's Hospital from August 2009 to August 2011. Patients included were less than 28 weeks postmenstrual age and were treated with caffeine for apnea of prematurity. Patients were excluded if they were older than 28 weeks postmenstrual age, receiving caffeine therapy for other indications, or experiencing apnea from other conditions, or if therapy was initiated more than 7 days after birth.

RESULTS A total of 89 neonates with a mean birth weight of 0.844 kg (range: 0.391 to 1.306 kg) and median gestational age of 26 2/7 weeks (range: 23 to 27 6/7 weeks) were evaluated. The median initial maintenance dose of caffeine citrate was 7.9 mg/kg/day, and 94.1% of neonates receiving ≤7.9 mg/kg/day required a clinical intervention during therapy compared with 76.3% in those receiving >7.9 mg/kg/day. Absolute incidence of tachycardia was low, and caffeine levels collected ranged from 16.6 to 34.4 µg/mL.

CONCLUSIONS In neonates less than 28 weeks gestational age, doses of caffeine citrate greater than 7.9 mg/kg/day are safe and are associated with a decreased need for clinical interventions.

INDEX TERMS apnea, caffeine citrate, dosing, neonates, tachycardia

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INTRODUCTION

Apnea of prematurity, defined by the American Academy of Pediatrics as a pause in breathing of greater than 20 seconds, or less than 20 seconds if accompanied by bradycardia and/or cyanosis, is one of the most common respiratory problems in the neonatal intensive care unit.[1,2] If prolonged, apnea can lead to hypoxemia of the developing brain and other organs. Incidence of apnea of prematurity is directly related to gestational age, with apnea occurring in approximately 80% of neonates weighing less than 1000 g at birth.[2,3] Advances in neonatal care in recent decades has resulted in an increased survival rate in low-birth-weight premature neonates, and therefore the number of neonates with this disorder is increasing.[2]

In addition to nonpharmacologic therapies such as bubble continuous positive airway pressure, therapy with methylxanthine class agents, which includes aminophylline, theophylline, and caffeine, has been shown to reduce the frequency of apnea and the need for mechanical ventilation[4] and have been used as respiratory stimulants for premature neonates for more than 30 years, and as of 2005, caffeine was one of the 10 medications most frequently prescribed in neonatal intensive care units.[5] The mechanism of action of caffeine is not fully understood; however, it is thought to act as a central nervous system stimulant by increasing the medullary respiratory sensitivity to carbon dioxide, thereby stimulating central inspiratory drive, and also through its competitive antagonism of adenosine at the cell surface receptor in the medulla.[6,7] Although highly effective for the management of apnea of prematurity, caffeine is not without adverse effects in neonates, including tachycardia, vomiting, and feeding intolerance.[2] Of the methylxanthine agents, caffeine is the preferred agent because of its higher therapeutic ratio, longer half-life, and

more reliable absorption when administered orally.[2] Other studies have looked at the effects of caffeine treatment on the incidence of apnea, effects of prophylactic caffeine dosing in neonates at risk for having apnea, and utilization during planned extubation to prevent reintubation.[4,8,9] Regardless of the indication, the dosing regimen used in the most of these studies was a loading dose of caffeine citrate, 20 mg/kg/dose, and then maintenance doses, 2.5 to 10 mg/kg/day once daily.[4,8,9] Despite a large amount of information on caffeine therapy for apnea of prematurity, there is minimal information on the response rate relative to maintenance doses and gestational age. [2,3]

The primary outcome of this retrospective analysis was to examine the relationships between initial maintenance dose of caffeine citrate therapy and gestational age and to determine the safety of higher maintenance doses in the management of apnea of prematurity.

MATERIALS AND METHODS

Study Population

This study was a retrospective analysis conducted to evaluate caffeine citrate therapy in neonates from August 24, 2009, to August 24, 2011. Patients were included if their postmenstrual age was less than 28 weeks at the time of caffeine citrate initiation and the primary indication was apnea of prematurity. Caffeine citrate therapy is initiated at North Carolina Children's Hospital for nonintubated neonates less than 28 weeks and experiencing >2 episodes of apnea requiring positive pressure ventilation, >6 episodes requiring any type of stimulation, or >8 episodes including self-resolving episodes. Patients were excluded if they were ≥28 weeks postmenstrual age, receiving caffeine citrate therapy for other indications (planned extubation withing the next 24 hours), apnea due to other causes (infection, neurologic abnormality, and reflux), and/or if caffeine citrate was initiated more than 7 days after birth. The Institutional Review Board of the University of North Carolina (UNC) Hospitals and Clinics approved the study.

Study Design

Patient data were collected from electronic medical records (WebCIS UNC Healthcare System, Chapel Hill, NC) and pharmacy information system (Cerner PharmNet, North Kansas City, MO). Parameters collected included 1) gestational age, 2) birth weight, 3) loading dose, 4) initial maintenance dose, 5) episodes of apnea, bradycardia, and desaturation (ABD) in the daily progress note, 6) number of weight adjustments (defined as dose changes to maintain initial maintenance dose [mg/kg/day] as neonatal weight increased), 7) number of maintenance dose increases (defined as an increase in the initial maintenance dose [mg/kg/dose] related to increasing apneic events), 8) number of mini-loading doses (defined as one-time only doses below the typical loading dose of 20 mg/kg and related to increasing apneic events), 9) reported tachycardia (defined as a heart rate greater than 180 beats per minute), and 10) caffeine-serum concentrations. Additional data collected included physician at initiation of therapy, number of septic work-ups during caffeine citrate therapy, final maintenance dose (mg/kg/dose), and postmenstrual age at discontinuation.

Study groups were determined by breakpoints in the data, and consistency medians was used to determine the comparison groups. For example, patients were separated into two groups based on whether their initial maintenance dose was above, equal to, or below the median maintenance dose of 7.9 mg/kg/day.

Statistical Analysis

Baseline characteristics of the study population were evaluated through descriptive statistics. The two-sample Wilcoxon rank-sum test was used to evaluate the patient demographics based on initial maintenance dose and weight at caffeine initiation.

RESULTS

A total of 184 infants were evaluated; 95 infants were excluded based on postmenstrual age ≥28 weeks, receipt of caffeine for indications other than apnea of prematurity, or if therapy was initiated >7 days after birth; and 89 infants were included in the analysis. Baseline characteristics are shown in Table. Mean gestational age was 26 weeks (range, 23 to 27 weeks), 51% were females, and mean birth weight was 0.844 kg (range, 0.391 to 1.306 kg). The median loading dose of caffeine citrate was 20 mg/kg (range 18.9 to 30.5 mg/kg) (Figure 1). The initial maintenance dose most frequently chosen was 8 mg/kg in 25

Table 1. Patient Baseline Characteristics (n = 89)

Characteristic	Results
Gestational Age – weeks	26 ± 1.2*
Birth Weight – kg	0.844 ± 0.21*
Female sex – no. (%)	45 (50.6%)
Loading Dose – mg/kg	20, 18.9 - 30.5†
Initial Maintenance Dose – mg/kg/day	7.9, 4.8 - 10.8†

** Mean ± standard deviation*
† Median, range

study infants, with a median initial maintenance dose of 7.9 mg/kg/day (range, 4.8 to 10.8 mg/kg/day) (Figure 2). A total of nine physicians were included in our analysis, and eight of nine prescribed >8.9 mg/kg/day.

When we evaluated patients based on median initial maintenance dose, 51 patients (range, 24.14 to 27.86 weeks old) were started on ≤7.9 mg/kg (low dose) compared to 38 patients (range, 23.29 to 27.86 weeks old) who were started on >7.9 mg/kg (high dose) of caffeine. In examining gestational age, the most frequent gestational ages at which caffeine therapy was initiated were 175 days (25 weeks), 182 days (26 weeks), and 194 days (27.71 weeks). When evaluating patients based on median gestational age, we found that 46 patients were ≤184 days old (26.26 weeks) compared to 43 patients who were >184 days old (26.29 weeks) (Figure 3).

The primary efficacy outcome of this study was to determine the correlation between initial caffeine maintenance dose and response rates. Because apneic events were not consistently documented by the providers as a means of evaluating dose-related response to therapy, the number of clinical interventions needed (weight adjustment, mini-loading, or maintenance dose increases from initial) was utilized as a marker of efficacy.

Weight adjustments at North Carolina Children's Hospital within the clinical guidelines advise practitioners to adjust maintenance doses as needed based on patient response. These dose adjustments were not typically performed unless the patient was continuing to experience apneic events. Therapy is typically continued until 32 to 34 weeks age, and it is common practice at North Carolina Children's Hospital to allow the patient to outgrow their maintenance dose. Mini-load doses ranged widely from 1.2 to 15 mg/kg based on physician preference.

Of the 89 infants included in the analysis, 94.1% of the low-dose group required a clinical intervention during the course of therapy compared to 76.3% in the high-dose group. When we evaluated the number of dose increases, 55 infants in the low-dose group required interventions, which was significantly more than the 19 infants who required interventions in the high-dose (p=0.0098) (Figure 4). There were also more weight adjustments (110 in the low-dose group compared to 79 in the high-dose group; p=0.84)

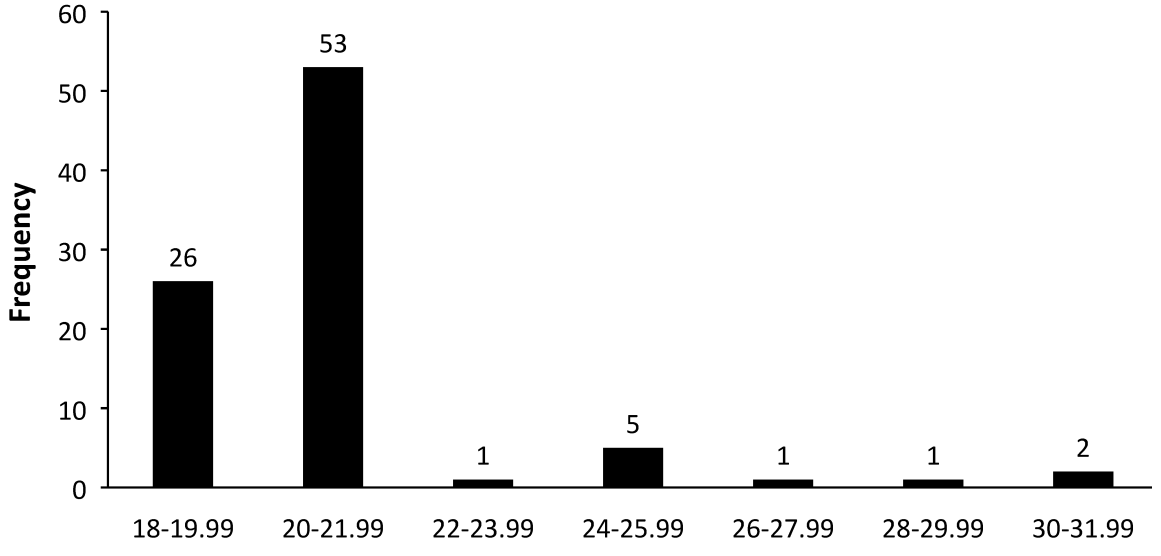

Figure 1. Initial Caffeine Loading Dose (mg/kg)

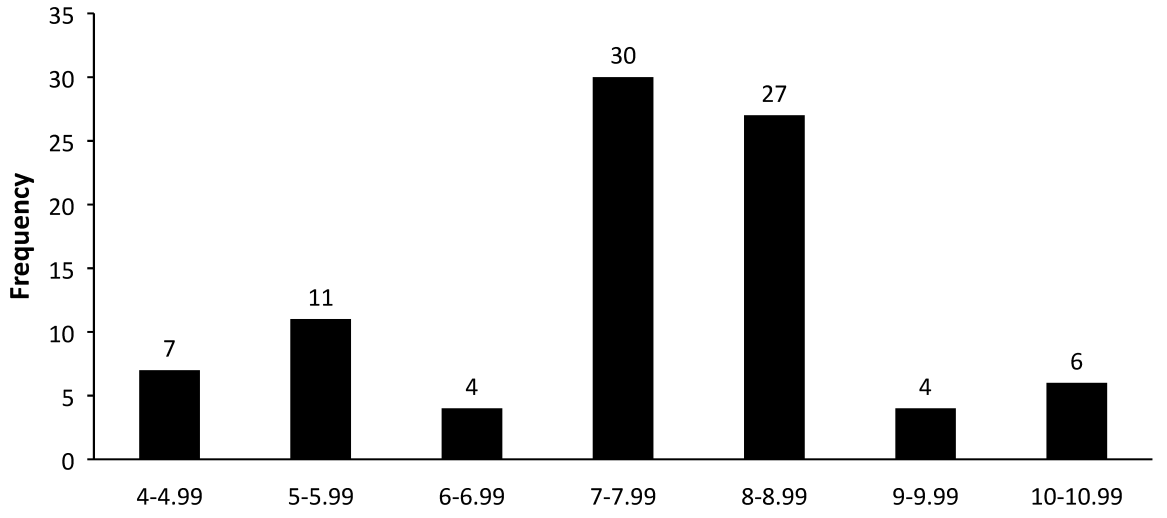

Figure 2. Initial Caffeine Maintenance Dose (mg/kg)

and mini-loads (43 in the low-dose group compared with 16 in the high-dose group; p=0.13); however, these findings were not statistically significant.

Of the 89 infants included in the analysis, 46 were ≤184 days (26.3 weeks) old, and 43 were >184 days (26.3 weeks) old. The younger group required significantly more weight adjustments (115 in the younger group compared to 74 in the older group; p=0.0053; Figure 5) and mini-loads (44 in the younger group compared to 15 in the older group; p=0.0315; Figure 6). They also required more maintenance dose increases (43 in the younger group compared to 31 in the older group; p=0.29); however this difference was not statistically significant.

Safety Outcome

Safety was evaluated in all 89 neonates included in this retrospective review, and the newborn intensive care center at North Carolina Children's Hospital advises practitioners to consider holding caffeine therapy for persistent episodes of tachycardia, defined as a heart rate greater than 180 beats per minute, without an alternative explanation. There was a low incidence of tachycardia in this analysis attributed to caffeine therapy, with 9 infants experiencing one episode

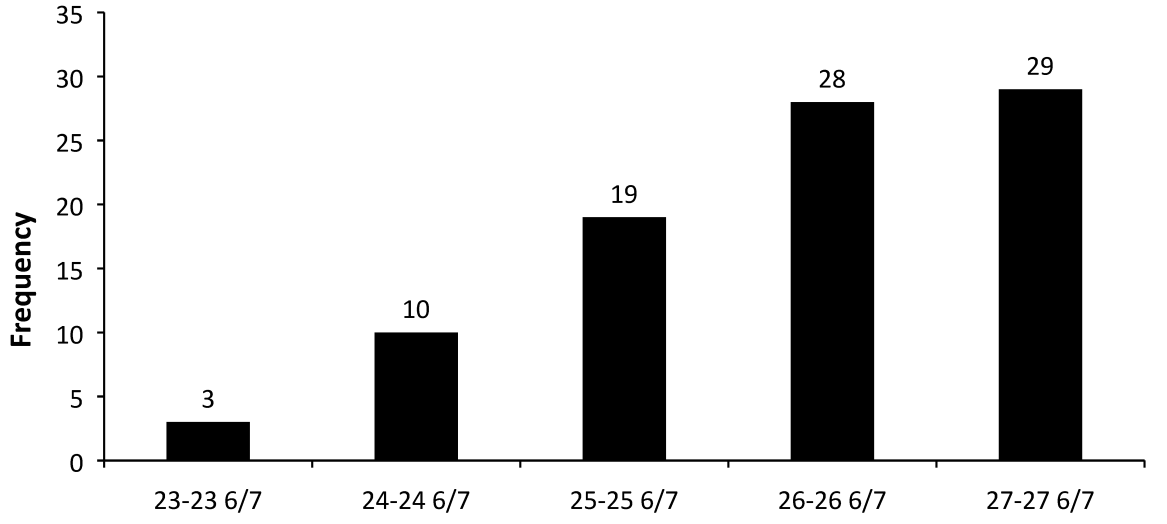

Figure 3. Gestational Age (weeks)

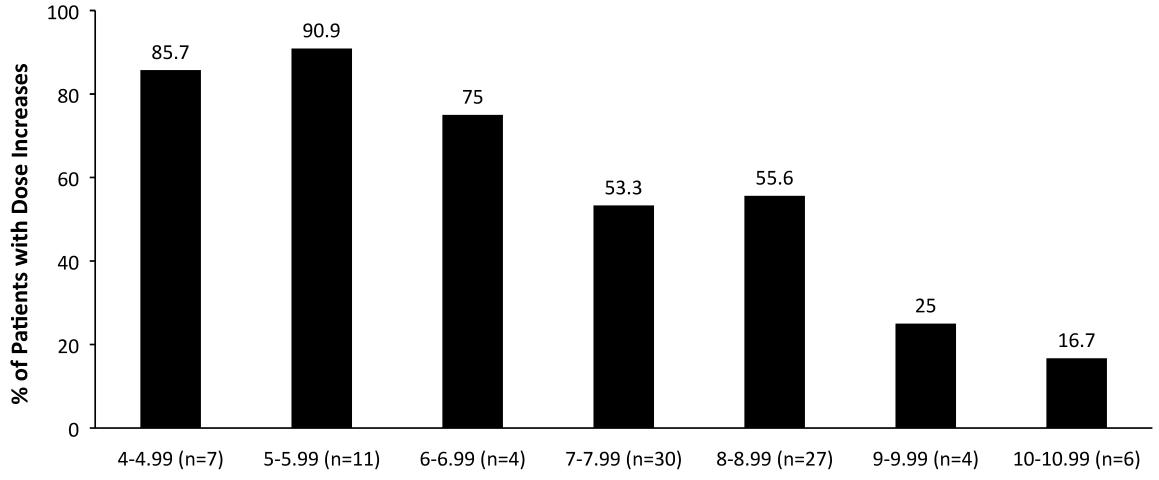

Figure 4. Relationship between Initial Caffeine Maintenance Dose and Maintenance Dose Increases

of tachycardia and 2 infants experiencing three episodes (Figure 7). In response to these events, 12 caffeine levels were drawn. Eleven of the 12 levels were drawn while the patient was at steady state on their current dose of caffeine, and all levels were drawn as troughs immediately prior to the next scheduled dose. Levels were drawn from 8 days to 6 weeks from the start of therapy at postmenstrual ages ranging from 28 to 31 weeks. Levels ranged from 16.6 to 34.4 mg/L, and UNC Hospital and Clinics' laboratory range for trough concentrations is 15 to 25 mg/L. However, the critical threshold for serious toxicity with caffeine therapy is >50 mg/L. Other adverse events including feeding intolerance and incidence of necrotizing enterocolitis were not assessed due to the retrospective nature of this review and lack of association in physician and nursing notes linking these adverse effects with caffeine therapy. Additionally, our data group had 32 patients with sepsis during caffeine therapy. Nineteen of those 32 patients were receiving ≤7.9 mg/kg/day, 10 patients were receiving 8 to 8.5 mg/kg/day, and 3 patients were receiving 9.6 to 10.2 mg/kg/day.

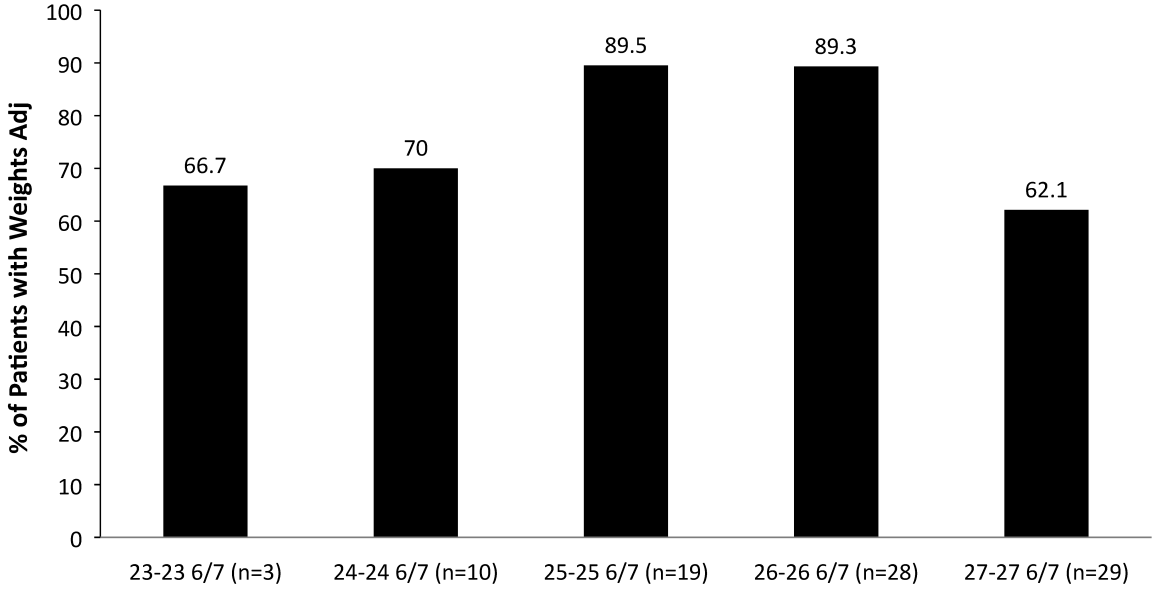

Figure 5. Relationship between Gestational Age and Maintenance Dose Weight Adjustments

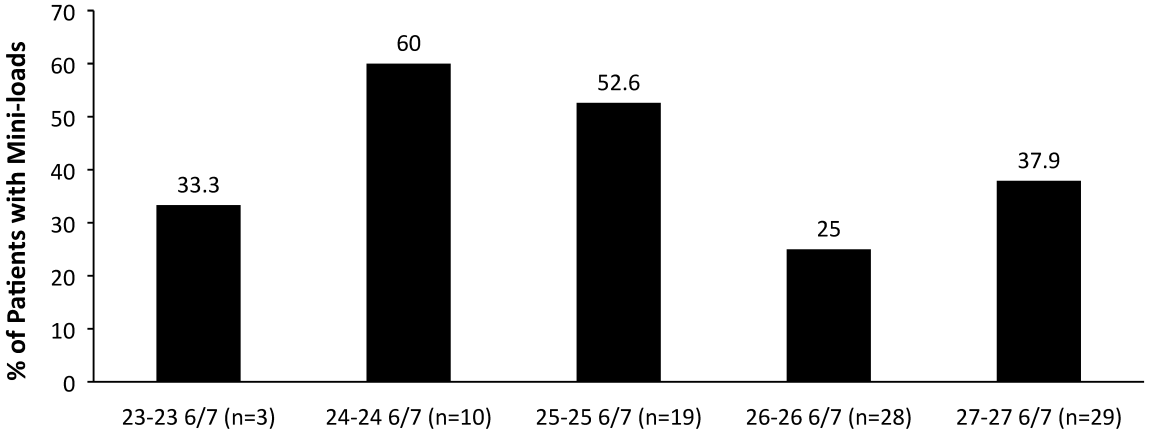

Figure 6. Relationship between Gestational Age and Mini-Load Requirement

DISCUSSION

The results of this study demonstrate that in the treatment of apnea of prematurity, lower initial maintenance doses of caffeine citrate are associated with the need for more clinical interventions, specifically more dose increases in neonates <28 weeks of age. Of note, our providers did begin initial maintenance doses at >7.9 mg/kg/day in 100% of our 23-week-old neonates (n=4). Also, lower postmenstrual age (less than 26.29 weeks) is associated with increased need for caffeine citrate weight adjustments and mini-loads, which is logical as these infants will require longer courses of therapy.

Occurrences of ABDs were recorded in the daily progress note and discussed daily for each patient receiving caffeine therapy. However, because of inconsistent reporting of ABDs in the notes and lack of nursing flow sheets in the discharge summary, the authors felt that this was an unreliable source of information to use to evaluate caffeine therapy. Because of the time period reviewed, nurses now record all ABDs in an electronic flow sheet. Unfortunately, previous studies have reported nurse identification and charting as an inaccurate method of data collection.[10] Respiratory probes are also used in many institutions as a means of measuring apneic events; however, there are limitations to their use if the sensor is based on chest wall movement and is therefore unable to identify an obstructive apnea where movement continues despite lack of airflow. Due to the retrospective nature of these data, we are unable to compare data sensed by the respiratory probe with the nurse-documented number of events. On a daily basis, our clinicians review the previous 24 hours of data on the respiratory monitor as well as nurse documentation of events in order to help distinguish ABDs that may have been obstructive from those that are caused by central apnea. Clinical interventions were consistently documented throughout the course of therapy and were deemed to be an appropriate surrogate marker of efficacy.

Caffeine dosing and the role of therapeutic drug monitoring of caffeine vary from practice to practice. Pharmacokinetic studies in neonates <30 weeks receiving caffeine citrate maintenance doses of up to 30 mg/kg suggest that caffeine clearance may be decreased in lower-gestation-aged neonates but that because of the general safety and tolerability of this drug, therapeutic drug monitoring may not be necessary.[11,12] Additional studies have suggested that because of decreased drug clearance, a maintenance dose of 5 mg/kg is sufficient for achieving target caffeine concentrations.[13]

However, the decision to adjust caffeine dosing based on drug levels remains a controversial topic, and clinical signs of caffeine efficacy and toxicity may be an appropriate alternative. One study of preterm neonates receiving doses of 2.5 to 0.9 mg/kg/day of caffeine citrate evaluated the role of caffeine level monitoring and concluded that therapeutic plasma levels between 5 and 20 mg/L are achieved in most preterm neonates regardless of gestational age and maintenance dose.[9]

Current practice at the North Carolina Chil-

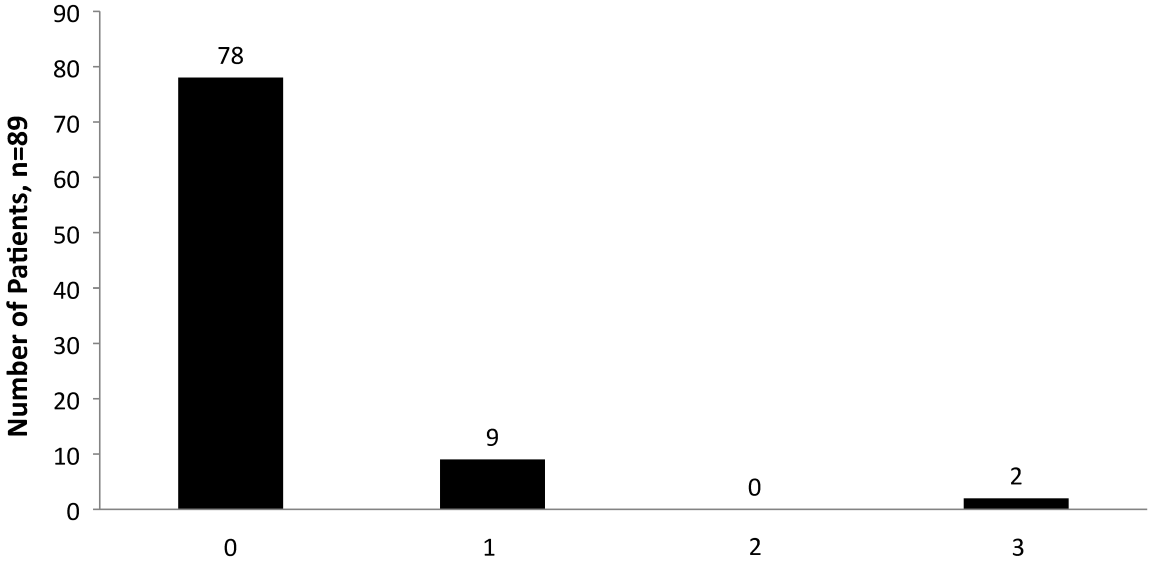

Figure 7. Episodes of Tachycardia

dren's Hospital is to not routinely monitor caffeine levels. Because an association among caffeine and feeding intolerance and necrotizing enterocolitis has not been identified, our research focused primarily on tachycardia as a measure of safety. At our institution, tachycardia is the main indicator for caffeine levels to be drawn, and doses are adjusted based on the patient's clinical response.

Based on these data, the authors feel that all neonates <28 weeks of age could be started on an initial maintenance dose of caffeine citrate of greater than 7.9 mg/kg/day to reduce the number of clinical interventions during hospitalization. Use of a larger initial maintenance dose may also help clinicians distinguish apnea resulting from subtherapeutic caffeine regimens from other potential causes including sepsis or changes in respiratory support.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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ABBREVIATIONS ABD, apnea, bradycardia, and desaturation; UNC, University of North Carolina.

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